Appendix F

White Paper on Measures for NCS Core Hypotheses

February 20, 2004

White Paper

On

Measures for NCS Core Hypotheses

by

Nancy Reiches, Amy Thomas, John Menkedick and Warren Strauss

BATTELLE
505 King Avenue
Columbus, OH 43201-2693

Contract No. 282-98-0019

Dr. Jim Quackenboss
Work Assignment Leader

Dr. Peter Scheidt
Project Officer

National Children's Study Program Office
National Institute for Child Health and Human Development
6100 Executive Blvd – 5C01
Rockville, MD 20892

Table of Contents

GLOSSARY F-6
INTRODUCTION F-10
DEFINITIONS F-10
    Measures F-11
    Methods for obtaining measures F-11
    Life Stages F-12
ROAD MAP FOR THE TABLES F-13
    List of Hypotheses F-13
    Outcome and Explanatory Variables (Table 1.0) F-13
    Table Describing Methods (Table 2.0) F-14
    Summary Table (Table 3.0) F-15
    Tables Describing Measures (Table 1.1.a through Table 5.7.g in Appendix B) F-15
I. DISCUSSION OF THE KEY MEASURES AND METHODS NEEDED TO SUPPORT THE NCS HYPOTHESES AND THE IMPACT ON SAMPLING DESIGN F-16
II. CONCLUSIONS AND RECOMMENDATIONS F-31
    Opportunities for Consolidation of Data Collection across Hypotheses F-33
    Opportunities for Reducing the Amount of Data Collection or Chemical Analysis by Sampling F-34
    Opportunities for Reducing the Burden of Data Collection by Collecting Less Precise Measures on the Majority of the Participants and More Precise Measures on a Small Validation Subset of the Participants F-34
References F-60

Appendix A: Hypotheses for the National Children's Study F-69
Appendix B: Proposed Measures for Hypotheses by Method, Lifestage, and Participant F-73

List of Tables

Table 1.0. Summary of Outcome and Explanatory Variables (Incidence or Prevalence where Available), Methods and Measures, Lifestages, Covariates for NCS Hypotheses F-36
Table 2.0 Measurement Methods and Timeline for Sampling for Hypotheses† F-43
Table 3.0 Summary of Measurement Methods and Timeline for Sampling for Priority Outcomes† F-53

GLOSSARY

ADHD – Attention Deficit Hyperactivity Disorder

Amniocentesis – Prenatal diagnosis method using cells in the amniotic fluid to determine the number and kind of chromosomes of the fetus and, when indicated, can serve as the basis for performing other biochemical studies.

Atopic dermatitis – also called eczema; a skin disorder characterized by itching, scaling, thickening of the skin; usually located on the face, elbows, knees, and arms.

Atrazine – a synthetic compound widely used as an agricultural herbicide; atrazine is thought to cause cancer and is banned in some European countries.

BMI – Body Mass Index; a relationship between weight and height that is associated with body fat and health risk. BMI = body weight in kilograms/height in meters squared

Bisphenol A – a synthetic organic compound used in the manufacture of epoxy resins and other polymers

Bronchoprovocation – a medical procedure used for evaluating asthma sensitivity

CNS – Central Nervous System

CP – cerebral palsy

Calicivirus – an RNA virus infecting cats; transmission occurs via air and mechanical contact

Carotenoids – a class of very important antioxidants produced by plants, which protects them from damage caused by free radicals produced during photosynthesis

Chest auscultation – examination with a stethoscope that reveals abnormal breath sounds, such as crackles that suggest fluid in the lungs

Clostridium – a genus of anaerobic bacteria that produce strong toxins and are responsible for diseases such as tetanus, botulism and gas gangrene

Cord blood – blood that remains in the umbilical cord and placenta following birth; rich source of stem cells

Cortisol – (hydrocortisone) a steroid hormone synthesized and released by the adrenal cortex of the adrenal glands; it is important for normal carbohydrate metabolism and response to stress

Cytokines – any of various proteins secreted by cells of the immune system that serve to regulate the immune system and control reactions between other cells

Dioxins – a primarily man-made chemical by-product formed during the manufacturing of other chemicals and during incineration; potent animal carcinogen, as well as the cause of severe weight loss, liver problems, kidney problems, birth defects, and death.

ER – Emergency Room

Endotoxin – a component of the membrane of gram-negative bacteria that is heat stable and toxic; a secreted toxin produced by bacteria is termed an "endotoxin"

Enterococci – a subgroup of the more general group of fecal streptococci bacteria

Genetic polymorphisms – difference in DNA sequence among individuals, groups, or populations (e.g., genes for blue eyes versus brown eyes)

Glucose metabolism – an index comprised of thresholds for the following five variables: abdominal obesity, elevated fasting blood triglycerides, low levels of HDL or "good" cholesterol, high fasting blood sugar (glucose) and high blood pressure; the clustering of certain metabolic-related heart disease risk factors

Glucokinase mutation – a subtype of diabetes, characterized by mild, persistent fasting hyperglycemia, a small increment in glucose in response to an oral load and a dominant family history; often an indicator of gestational diabetes

Glycemic index – a ranking of foods based on their immediate effect on blood sugar levels; measures how much your blood sugar increases over a period of two or three hours after a meal.

Hg – Mercury

HgbA1C – a laboratory test that reports average blood sugar level over the last 2 to 3 months; also called A1C, Hemoglobin A1C and Glycohemoglobin testing.

Hx – History, specifically medical history

IgE – a trace serum protein (antibody) associated with allergic reactions

IVH – Intraventricular Hemorrhage

Insulin gene VNTR – insulin-dependent diabetes mellitus gene

Insulin resistance – state in which the body does not respond to the action of insulin hormone although enough insulin is produced; may happen because the person is overweight and has too many fat cells, which do not respond well to insulin.

Interleukin – a cytokine secreted by immune cells that regulates a range of immune system functions; promotes the proliferation and activity of other immune cells

Lymphocytes – any of a group of white blood cells of crucial importance to the adaptive part of the body's immune system; the adaptive portion of the immune system mounts a tailor-made defense when dangerous invading organisms penetrate the body's general defenses.

Metallaproteinase – a member of a group of enzymes that can break down proteins

OP – organophosphate pesticide

Oxidant – a substance containing oxygen that reacts chemically in air to produce a new substance; the primary ingredient of photochemical smog

Pb – Lead

PCB – Polychlorinated biphenyls; a group of organic compounds that are highly toxic to aquatic life and persist in the environment for long periods of time

Paramixo – a virus that produces gastro-intestinal symptoms; often found on farms

Rotavirus – a virus that causes diarrhea; most common cause of infectious diarrhea in the United States, especially in children under 2 years old

SES – Socio-economic Status

Selenium – element that works with vitamin E as an antioxidant and binds with toxins in the body, rendering them harmless

Tanner stages – a sexual maturity rating; staging helps determine whether development is normal for a given age

Urine cotinine – A breakdown product (metabolite) of nicotine that can be measured in urine

Urine isoprostane – excellent molecular biomarkers for oxidant stress

VNTR – a region of human DNA with identifiable genetic sequences

WBC – White blood cell count; leukocyte count

WBV – Well Baby Visit

INTRODUCTION

The purpose of this White Paper is to provide the National Children's Study (NCS) Program Office at NICHD with a discussion of measures that have been proposed to test the current set of core hypotheses for the NCS and how they may impact the sampling design. In this paper we address each priority outcome and its corresponding hypotheses, the measures that have been suggested for each, the methods by which each measure could be obtained, and the study participants who will provide the data in question. More specifically, we address the following objectives:

- Identify the measures or group of related measures (e.g., demographic, socio-economic, biologic, and environmental measures) that will be required to test the priority outcomes and their respective hypotheses, as well as relevant covariates, confounders, or effect modifiers;
- Identify the general types of methods by which the data for each measure will be obtained, and where, e.g., interview at home, physical examination at physician office;
- Define the study participant from whom data will be obtained;
- Specify the life stages (relative to the index child) at which the required data will be sampled;
- Identify critical measures and methods that might affect the desirability of different design options available for the NCS; and
- Finally, make recommendations that might reduce the burden of sample collection and its attendant cost without compromising the ability to test the core hypotheses at the desired level of power and validity.

The information contained in this paper is presented with a careful review of the measures and methods that are required to address each of the NCS hypotheses, followed by a series of tables and explanatory comments that summarize the data collection methods that have been proposed to assess key measures across the NCS priority outcomes. As stated in the NCS Interagency Coordinating Committee (ICC) Priority Outcomes and Exposures document, the NCS is more than a set of related hypotheses, and there are basic measures that will be needed in addition to those required to test the hypotheses. However, the focus of this paper is on the measures needed for the hypotheses.

DEFINITIONS

Participants

Even though this study will focus on children, the measurements required to test the hypotheses of the National Children's Study will be derived from a variety of sources, including family members of the index child, and other individuals with whom the index child might interact. The tables presented here show data that will be obtained from the following participants.

- Index Child
- Biological Mother
- Biological Father
- Other Adult: Other adults can include primary caregivers, other adults who live in the same household, teachers or day care providers, or others who are knowledgeable about the index child

Measures

Measures are defined as the actual data values obtained from participants, or from a visual assessment or analysis of physical samples collected from a participant's environment. These will include, but not be limited to, biological measures, medical, demographic, social, residential, and occupational histories, physical examinations, and direct observations of behavior. For example, biological measures derived from blood would include serum glucose, blood pressure, lipid profiles, and many others. Demographic measures include age, race, sex, ethnicity, and are often related to residential and occupational histories. Occupational histories can yield measurements characterizing exposures to chemicals and other potential risk factors. Data resulting from direct observation from a medical professional will in many cases provide specific information about the health status of participants and the outcomes of interest in the index children, and are therefore, very important. For example, examinations by health professionals will be crucial in identifying birth defects, onset of puberty, preterm birth, and other key outcomes. In addition to measures obtained from participants, some hypotheses will require physical environmental sampling from a participant's residence or other place of activity, collected in a variety of media such as air, dust, and soil, and analyzed for chemical or biological contaminants.

Methods for obtaining measures

For the purposes of this White Paper, it is important to distinguish *measures*, as discussed above, from the general *methods* used to obtain these measures. The data that are presented in the tables in this document address both methods and measures, since they are closely interrelated. The method defines the procedure or the source by which a measure is obtained. We have clearly delineated between source and method – the method used may define the source in some context, but should not be a replacement for the source. In nearly all instances, multiple numbers of measures are associated with a single method. For example, venipuncture is the method used for obtaining blood samples. Stating only that a blood sample has been collected does not allow us to understand the measures involved and their potential relevance in testing one of the core hypotheses. Countless measures can be made from blood samples, assuming adequate quantities and storage, when appropriate. Understanding the methods helps us to understand the burden on study participants. As the tables that follow will demonstrate, blood is a primary source of data for many hypotheses. Understanding the use of these blood samples and the measures that will be made from them can have impact on the design of the study. In particular, the timing of blood draws is not always critical, but we still need to emphasize the timing criticality of many measurements. Therefore, where feasible, the suggested time for a blood draw could be changed to match up with the timing of a blood draw for another hypothesis. This concept could introduce logistic and cost efficiencies into the study and perhaps could increase participant retention by reducing the burden and minimal risk associated with venipuncture.

Other methods that will routinely be used across the core hypotheses include urine collection, other physical samples, direct observations by medical professionals including examinations or other technical medical procedures, reviews and data abstraction from medical records, and direct observations of behavior. Some methods may be specific technical procedures, e.g., vacuuming with a specified filter or use of sensors, designed to collect environment samples in the home or community, and these are noted as such in the detailed tables contained in Appendix B, but are largely excluded from the subject-specific methods for obtaining NCS data described in Tables 2 and 3.

Two other major methods are interviews and questionnaires. We assume that interviews will be conducted face-to-face or over the telephone by a trained interviewer. There is a distinction between face-to-face and telephone interviews in the level of detail and accuracy of information that can be obtained (e.g., use of visual prompts, response cards for sensitive questions) and the ability to make direct observations of the household and child (in face-to-face interviews). Questionnaires, by contrast, are self-administered - using paper and pencil instruments, web-based surveys, etc. Although interviews and questionnaires are similar, it is important to distinguish between them for several reasons. The greatest similarity between the two is that both collect self-reported data, bringing along all the potential limitations thereof, i.e., poor recall, intentional misinformation about sensitive topics, inability to interpret the questions correctly, etc. However, the costs and quality of information associated with these two data collection methods can vary significantly and may play a role in choosing one over the other for certain parts of the NCS. For example, some individuals will write down sensitive information, e.g., smoking, alcohol and drug usage, but be reluctant to tell an interviewer directly. On the other hand, skillful interviewers are often able to elicit valid information that might not be reported on a questionnaire. In the detailed tables of Appendix B, we provide separate summaries of proposed information collection via interviews and self-administered questionnaires. However, these two modes of data collection are combined in the summary tables (2 and 3) located in the main body of this report. This is appropriate, since the study planners have not decided between these two methods for most measures of this type.

Life Stages

Since the NCS will be a longitudinal study, definition of the life stages at which data will be collected is important. For most hypotheses, as the tables will demonstrate, the identified life stages relevant to the hypothesis are similar. In only a few instances are there substantial variations, and these are noted where appropriate.

In general, the earliest life stage is preconception. The relative importance of obtaining data prior to pregnancy varies among hypotheses and may have impact on study design and recruiting methods. For example, to test the effects of gestational diabetes in women whose glucose was normal prior to pregnancy demands that either pre-pregnancy measures are available or that retrospective assessment of pre-pregnancy diabetes status (with error) is acceptable to the NCS. For example, if no biological specimens prior to pregnancy are accessible, women could still be eligible on the basis of medical history or current self-reported data.

The three trimesters of pregnancy represent life stages that are fairly standard points for data measurement across nearly all hypotheses and, in many cases, will correspond with routine prenatal care, thus giving investigators an opportunity to increase retention throughout this period of time. The time surrounding birth is also identified as an important life stage, especially if outcome measures such as preterm births or certain birth defects need to be observed at that specific time. Similarly, some hypotheses may depend on difficult to obtain measures, such as those collected at birth in the delivery room (e.g., a culture of the placenta or umbilical cord). In the case of a stillbirth, autopsy results may be required in a timely fashion.

There is some variation across hypotheses in the time intervals recommended for data collection during the neonatal period (0-28 days) and the infancy period (up to 1 year). In most cases, it appears that the required information could be collected during routine well baby visits (WBV), which would again perhaps help with retention and cost elements of the study. After the first two or three years of life, most measures are required only on an annual basis or less frequently, e.g., sometime during years 7-9 or childhood, or once during adolescence. To the extent that many of the measures are not time dependent on life stage, or at least have a wide acceptable range, there are opportunities for efficiencies in design and data collection with regard to life stage.

ROAD MAP FOR THE TABLES

List of Hypotheses

In Appendix A (Hypotheses for the National Children's Study) we provide a list of the 21 hypotheses that thus far compose the National Children's Study. This is included as a reference as readers review the data throughout the document.

Outcome and Explanatory Variables (Table 1.0)

The importance of individual measures actually rests with their relationship to their respective hypotheses, since these are the elements that ultimately will be used to test the hypothesis. Therefore, we begin with a table that summarizes the primary outcome and explanatory variables for each hypothesis. (Table 1.0: Summary of Outcome and

Explanatory Variables (Incidence or Prevalence Where Available), Methods and Measures, Lifestages, Covariates for NCS Hypotheses) For each variable, we list the methods and measures that will be used to collect the data as well as the lifestages at which data will be collected. Where available, we also present the prevalence of the outcome and explanatory (risk factor) variables. In the final column, we provide a brief list of variables that may serve as covariates, confounders, or effect modifiers, and therefore should be measured in the course of data collection. This table is not intended to be a comprehensive list of every measure that will be obtained over time. Rather, its intent is to serve as a reference for the primary variables of interest and the ways in which they may be obtained. Additional detail is given in later tables.

Table Describing Methods (Table 2.0)

The next major table, entitled "Measurement Methods and Timeline for Sampling for NCS Hypotheses) is method based. It summarizes the methods that are expected to be required to collect the data across all the hypotheses and indicates the participant from whom the data will be obtained. While Table 2.0 is helpful, it is potentially premature since the study planners have not determined most of the methods that the NCS will utilize. Each lifestage in the study is represented. In each cell, we use the abbreviations "M" for Mother, "F" for Biological Father, "C" for Index Child, and "A" for Other Adult. These tables are useful visualizations to assess the degree of burden across subjects, but not the specific importance of a set of measures for testing a hypothesis.

The location where each measurement method will generally be collected is indicated in the matrix below.

Method	Location
Blood	Medical office, clinic, or home visit
Urine	
Direct Observation	
Other Physical Sampling	Examples include: Medical office or clinic for ultrasound exams, Residence, daycare, school, and worksite for detailed environmental sampling
Medical Record Review	Performed by NCS staff
Interview/ Questionnaire	Home (whether conducted in person, by telephone, or self-administered)

In many cases, questionnaire and interview information is desired from the index child during early lifestages when an adult will need to provide the responses. The entries in Table 2.0 however correspond to the study participant that is the focus of the questions, even though technically it might be the mother, father, primary caregiver, or other responsible adult providing the actual responses for the index child. We chose to display the information in this manner because of our uncertainty regarding a specific lifestage that can be assumed for when the index child can provide her own information. The age at which a child can answer accurately for herself has not been determined, and may vary for each individual. In the detailed tables of Appendix B, we do provide some insight into who might provide the proxy responses for the index child for several of the hypotheses.

Finally, Table 2 provides an overview of information and samples that are to be collected from human subjects participating in the National Children's Study. Several Core Hypotheses, including those that relate to neuro-cognitive outcomes, injury, and asthma, also require the collection of environmental samples from areas in which the pregnant mother or index child spend time (for at least a subset of the study population). These samples are not included in Table 2.0 (or Table 3.0), but can also add to the burden of study participants and increase other demands on the study that would affect the sampling design. (Environmental samples are included in the more detailed tables in Appendix B.)

Summary Table (Table 3.0)

In this table, "Summary Measurement Methods and Timeline for Sampling for Priority Outcomes," we move away from the pattern of looking at specific hypotheses and summarize the methods of data collection at the priority outcome level. This table provides a quick look at the methods that will be required across the board. For example, one could determine if blood samples will be uniformly required for a given priority outcome and its respective hypotheses, and this information may be useful in planning the logistics of data collection, analysis, and possible storage. Also, the table provides a quick look across hypotheses, whereby one could determine, for example, that blood samples from the Mother are required during the 2^{nd} trimester of pregnancy, irrespective of core hypothesis. This table has similar entry formatting to Table 2.0 with respect to proxy information provided for the index child in interviews and questionnaires.

Tables Describing Measures (Table 1.1.a through Table 5.7.g in Appendix B)

This is an extensive set of tables detailing the measures which may be used for each hypothesis.

- For each hypothesis, we present seven tables, one for each method of data collection. They are presented in the following order: Blood, Urine, Physical Sampling (other than blood and urine), Medical Record Review, Interview, Self Administered Questionnaire, and Direct Observation by a Medical Professional. The collection of biological specimens other than blood or urine in subsumed in the Physical Sampling category, as is collection of environmental samples. These may be collected by medical professionals or trained study staff.

- The numbering scheme for the tables reflects both the hypothesis and method of data collection addressed in the table. The scheme follows the pattern N.N.x, where N.N represents the number of the hypothesis, and the letters "a" through "g" represent the method of data collection, as specified in the bullet point above.

- At the beginning of the tables for each section, we identify the hypothesis and provide a list of references that apply to that section.

- Each table lists the names of the measures to be collected by the method addressed by that table, organized by participant and lifestage. If no data are required for a given method, that is noted.

- Following each table are brief comments about the priority of the measures for testing the hypothesis in question and in some cases recommendations about possible combinations of data collection with other hypotheses.

- Measures in bold are of critical importance or high priority. These are the variables without which the given hypothesis cannot be adequately assessed (i.e., the primary outcome variable or primary risk factor of interest). Those of lesser importance are italicized.

I. DISCUSSION OF THE KEY MEASURES AND METHODS NEEDED TO SUPPORT THE NCS HYPOTHESES AND THE IMPACT ON SAMPLING DESIGN

The following text provides a discussion of the key measures and methods expected to be collected to support each of the NCS hypotheses. Each description provides an overview of the response variable of interest, the main explanatory variables, variables necessary to apply appropriate exclusion criteria related to the research objective, and a description of any important covariates or confounders to be taken into account for each NCS hypothesis. In addition, information is provided about the impact that specific measures might have on the sampling design for the NCS, as well as strategies that the NCS might consider to reduce the data collection burden across the majority of the study population when appropriate. The information contained in this text corresponds directly to the detailed tables provided in Appendix B. Note that the following text and tables in Appendix B present a first attempt to look at measures across hypotheses. These are not the only measures that will be used in the NCS, and they do not represent decisions that have been made by the study planners on what measures are required and when they should be collected.

Hypothesis 1.1 of the National Children's Study focuses on the relationship between impaired glucose metabolism during pregnancy among women without diabetes prior to pregnancy and risk of major congenital malformations of the heart, central nervous system, musculoskeletal system and all birth defects combined. This hypothesis has multiple adverse health outcomes of interest, each of which relate to the presence or absence of a birth defect. It is assumed that all birth defects will be recorded via direct observation of the index child by NCS medical data collectors or through an interview with a responsible adult (parent or primary caregiver during early lifestages, or the index child at later lifestages) with confirmation of diagnosis via medical record abstraction or appropriate physical testing, e.g., genetic tests. While many birth defects will be apparent through direct observation in early lifestages, some birth defects such as congenital malformations of the heart may not become apparent until later stages of life, perhaps as late as early adulthood (e.g., 18 years of age). Based on the assumption of an NCS sample representative of the general U.S. population, we would expect to observe approximately 3% of the study population with some type of birth defect, with 0.6% of the NCS population having congenital heart defects and 0.6% having birth defects related to the central nervous system (Martinex-Frias, 1998). The very low anticipated prevalence of birth defects combined with the possibility that some birth defects may not be diagnosed until later in life have strong implications on the sampling design for the NCS – as it will be very important to have strong retention rates in this study (through early adulthood) in order to address this hypothesis with sufficient power.

Only a subset of the NCS study population would be appropriate for testing Hypothesis 1.1 – namely those children whose biological mothers did not have diabetes prior to pregnancy. Based on statistics from the CDC, approximately 2% of women aged 20-39 have diabetes, which conceptually leaves the majority of the NCS study population available to assess this hypothesis. However, confirmation of a pre-pregnancy diagnosis of diabetes may be operationally problematic, requiring either a preconception sample to formally apply this exclusion criterion, or some assumptions on the reliability of retrospective measures of preconception diabetes status for women recruited into the study after conception. For example, while not perfect, a strategy could be employed to address this hypothesis by excluding only those women who were known to have a positive diagnosis of diabetes prior to pregnancy (either through self reporting or medical history abstraction). A validation study could then be performed on a subset of women enrolled prior to conception to estimate the percentage of women who test positive for diabetes without previously having been diagnosed so that appropriate statistical adjustments could be made to correct for any biases introduced into the relationships due to error in including a fraction of women who had diabetes prior to pregnancy in the assessment for this hypothesis.

While it may be possible to design a strategy for excluding women with pre-pregnancy diabetes based on retrospective measures, the main explanatory variable for Hypothesis 1.1 must be assessed during pregnancy. Impaired glucose metabolism during pregnancy can be assessed using multiple measures from venous samples of blood collected from the mother during routine prenatal visits. These measures include glucose tolerance, blood glucose concentration, and serum insulin concentration. Since Hypothesis 1.1 relates to measures of impaired glucose metabolism during pregnancy, it will be important to understand how these measures are likely to vary over the course of pregnancy. A validation study that assesses the amount of temporal variability (daily, weekly, monthly) in these key explanatory measures among a small sample of pregnant women combined with the use of statistical methods that correct for measurement error in explanatory variables might allow investigators to reduce the data collection burden on the main NCS cohort to a single blood sample collected during pregnancy to address this hypothesis. The extent to which these measures of impaired glucose metabolism can be assessed from stored or archived samples of blood may also open up other avenues of efficiency through the use of outcome dependent sampling from within the NCS cohort. This might entail the conduct of a matched case-control study from within the NCS cohort in which a much smaller and efficient sample of children with and without birth defects is used to address this hypothesis. Due to the very low prevalence of birth defects, we would recommend collecting at least one blood sample during pregnancy for as many NCS participants as possible. However, by relying on archived blood samples in an outcome dependent sampling design for this hypothesis, there could be large savings in the cost of chemical analysis of these blood samples.

In addition to the direct measures of impaired glucose metabolism, there are other measures from blood samples collected during pregnancy that may be important in assessing this hypothesis, including HgbA1C, lipid profile, insulin gene VNTR, glucokinase mutation, and hormone levels such as cortisol. These additional measures may act as effect modifiers or confounders for the main explanatory variable. Other measures that are important for this hypothesis would include genetic testing, smoking status, use of medication, family history, and other factors that are known to be related to birth defects. For a summary of the specific measures that are considered important for addressing Hypothesis 1.1, please see Tables 1.1a – 1.1g in Appendix B of this report.

Hypothesis 1.2 of the National Children's Study tests whether intrauterine exposure to mediators of inflammation due to infection of either vaginal, cervical, or uterine sites, or more distal sites (e.g., periodontal disease) is associated with an increased risk of pre-term birth. The primary outcome of interest is pre-term birth, defined as gestation less than 37 weeks. While gestational age at birth may be readily estimated in most cases, gestational age is uncertain in some pregnancies. In these cases, birth weight, a routine assessment as part of the newborn physical exam, could serve as a surrogate measure for pre-term birth. According to statistics from the CDC, we can expect approximately 2% of children in the study population to be born pre-term, assuming the NCS sample is representative of the general U.S. population (CDC, 2003).

Based on statistics from Andrews (2000), approximately 2% of pregnant women contract an intrauterine infection. The prevalence of periodontal disease in pregnant women is not known precisely, but is anticipated to be very low. The eyes, ears, and sinus cavities are other examples of distal sites susceptible to infection which may require medication. Occurrence of distal infections during pregnancy might be assessed through interview.

Assessing intrauterine exposure to mediators of inflammation due to infection of either vaginal, cervical, uterine, or distal sites requires the collection of infection data, as the primary explanatory variable, during pregnancy and at birth. Interviews with the mother can also reveal whether any infections occurred during pregnancy, and medicine usage can be determined by review of the mother's medical record. Treatment of infection through over-the-counter medications is not common, but interviews with the mother can include questions about usage of over-the-counter drugs and untreated mild or self-limiting infections, such as colds. Infections of the mother's teeth and gums can be observed through dental exams. Venous samples of blood collected from the mother during routine prenatal visits as well as at birth can provide measures of WBC, antibodies, and genetic markers NOS. Vaginal swab samples collected from the mother during pregnancy can indicate the presence of cytokines and metalloproteinase. Physical examination of the index child and the placenta at birth to analyze for antibodies and cytokines can provide additional measures for assessing intrauterine exposure to mediators of inflammation due to infection.

Since Hypothesis 1.2 relates to measures of infection during pregnancy, it will be important to understand how these measures are likely to vary over the course of pregnancy. To reduce the burden of collecting vaginal swab samples each trimester of pregnancy to address Hypothesis 1.2, investigators might be able to employ a validation study that assesses the amount of temporal variability in the key explanatory measures among a small sample of pregnant women, combined with the use of statistical methods that correct for measurement error in explanatory variables. This would allow investigators to reduce the data collection burden for this hypothesis to a single swab sample collected during pregnancy from the main NCS cohort. Due to the very low prevalence of pre-term births, we would recommend collecting at least one swab sample during pregnancy from as many NCS participants as possible. This sample could be collected as part of the routine prenatal examinations conducted over the course of pregnancy (prenatal examinations are generally performed once a month and increased to once a week in the final month, with internal examinations conducted during the initial exam and in the final weeks of pregnancy, or as needed). Similar methods could be used to reduce the number of dental exams required during pregnancy to support this hypothesis. Routine oral health care would normally include at least one dental exam during pregnancy. Because gingivitis, an early stage of periodontal disease in which the gums may become red and swollen, is especially common during the second to eighth months of pregnancy, dentists may recommend more frequent cleanings for women in their second trimester or early third trimester of pregnancy to help avoid gum problems (ADA, 2004).

Additional measures that may be important in assessing this hypothesis include: economic status, race/ethnicity, and mother's medical history. These measures may act as effect modifiers or confounders for the main explanatory variable. For a summary of the specific measures that are considered important for addressing Hypothesis 1.2, please see Tables 1.2a – 1.2g in Appendix B of this report.

Hypothesis 2.1 of the National Children's Study tests whether repeated low-level exposure to nonpersistent pesticides *in utero* or postnatally increases risk of poor performance on neurobehavioral and cognitive examinations during infancy and later in childhood, especially for certain agents, among those with genetically decreased paraoxonase activity. The response variables of interest for testing this hypothesis represent measures from neurobehavioral and cognitive examinations. Appropriate developmental measures for the NCS as a function of life-stage are the focus of a pilot study recently initiated by the NCS Program Office. While the recommended battery of tests for assessing neurobehavioral and cognitive functions at different stages of development as part of the NCS are not yet fully developed and specified, these tests are likely to be performed in a clinical setting on the index child at various points in time. Some of these tests are likely to be time consuming and costly to implement – which could have an impact on the sampling design. Also, some tests will only be feasible for latter stages of development, which might place important demands on the retention of study subjects (particularly for those that had undergone genetic testing and detailed environmental sampling in support of this particular hypothesis).

As stated, this hypothesis draws a distinction about the potential effects of nonpersistent pesticides on neurobehavioral and cognitive development among children with genetically decreased paraoxonase activity. The precise prevalence of this condition in the general population is not known, but is expected to be very small (Eskanazi, 1999). Genetically decreased paraoxonase activity can be assessed in NCS participants via appropriate laboratory testing. For this hypothesis, we regard the measure of genetically decreased paraoxonase activity as a potential effect modifier for the relationship between neurobehavioral and cognitive development and exposure to non-persistent pesticides – with potentially greater risk of neuro-cognitive deficits among those with decreased paraoxonase activity and higher exposure to non-persistent pesticides *in utero*. Genetic testing for paraoxonase activity might be used to select subjects for more extensive environmental and health monitoring.

Assessing both prenatal and postnatal exposure to targeted non-persistent pesticides with a high degree of precision and accuracy among NCS study participants will be a costly and burdensome task – and may not be feasible to complete for the main cohort of women and children participating in the study. Accurate and precise exposure assessment for these types of chemicals involves detailed study of multiple microenvironments (e.g. home, work, day-care), multiple routes of exposure (air, dietary ingestion, non-dietary ingestion, and dermal), multiple time periods (given that residential pesticide usage and dietary intake may be intermittent), and activity patterns (location, heart rate, etc.). In addition, due to the fact that this hypothesis focuses on nonpersistent pesticides, it will be important to understand how exposure may vary in study participants over time. Unlike persistent pesticides such as PCBs that stay in the blood and other body tissue for long periods of time following exposure, nonpersistent pesticides and their metabolites tend to have very short residence times in blood and urine. Therefore, it is highly probable, with limited NCS resources for exposure assessment, that study participants will have high exposure events that go unrecorded in this study, even with the collection and chemical analysis of multiple blood and/or urine samples for each study subject.

As part of a pilot study in support of the NCS, EPA's National Exposure Research Laboratory and Battelle worked collaboratively to develop some statistical study design guidelines for capturing exposure assessment information to support NCS hypotheses such as this one that requires information related to difficult to measure exposure events. Results of this pilot study suggested that by using sophisticated statistical models that account for measurement error in explanatory variables, the burden of environmental exposure assessment could be substantially reduced for the majority of study participants.

For example, to support the prenatal exposures to non-persistent pesticides for this research objective, the majority of study participants (pregnant women) would only be required to provide a single urine sample and perhaps some detailed information related to activity patterns, diet, and consumer product use (including pesticide products) over the course of their pregnancy. However, a sub-sample of NCS study participants would be asked to undergo an additional rigorous environmental assessment protocol during their pregnancy to establish both the temporal variability in non-persistent pesticide exposure and the relationship between the precise measures from the aggregate exposure assessment and the reduced information that is collected from the majority of study participants. Additional details regarding this pilot study and the design guidelines that were recommended for the exposure assessment portion of the NCS can be found in a series of reports (Strauss et al., 2003).

In addition to the response variables related to poor performance on neurobehavioral and cognitive examinations, the main effects of prenatal and postnatal pesticide exposure, and the potential effect modifier of genetically decreased paraoxonase activity, there are a variety of covariates and potential confounders that are important to assess in support of Hypothesis 2.1. These may include such factors as socio-economic status, parental education, exposure to other neurotoxins such lead, mercury, and persistent pesticides, residential and daycare environment, and nutrition. For a summary of the specific measures that are considered important for addressing Hypothesis 2.1, please see Tables 2.1a – 2.1g in Appendix B of this report.

Hypothesis 2.2 of the National Children's Study assesses whether prenatal infection and mediators of inflammation are risk factors for neurodevelopmental disabilities, such as cerebral palsy and autism. Primary outcomes will be assessed by the presence or absence of neurodevelopmental disabilities, as observed through physical and neurological examinations. According to statistics from the CDC (2003), we can expect to observe cerebral palsy in approximately 0.2% of children in the study population and autism in approximately 0.3% of children in the study population by age 3, assuming the NCS sample is representative of the general U.S. population. The very low prevalence of these disabilities has strong implications on the sampling design for NCS – retention of NCS index children will be important to address this hypothesis with sufficient power. In particular, it will be important to retain the maximum number of children at least to or beyond the average age of diagnosis for these disorders (e.g., age 6 or 7). In addition, the necessity of umbilical cord blood samples or samples taken early in infancy may have a very strong impact on the study design, as there would need to be coordination with medical professionals performing the delivery of the index child and its neonatal treatment. Data on prenatal infection and mediators of inflammation comprise the main explanatory variables. Critical measures for assessing prenatal infection and mediators of inflammation will be collected from the mother during pregnancy and/or at birth. These include: vaginal, cervical, and placental cultures; interleukins, cytokines, genetic and inflammatory markers, and infection serology assessed from blood samples. Analysis of the amniotic fluid and umbilical cord blood at birth will provide additional measures of risk factors for neurodevelopmental disabilities. Neurological examinations of the index child through age 7 will also be important for assessing the primary outcome (cerebral palsy and autism are normally diagnosed in early childhood). The frequency and invasiveness of some data collection procedures may place a high burden on NCS subjects that impacts the sampling design for NCS.

In addition to the primary response variables, mother's medical and obstetrical history, as well as family history, may be important in assessing this hypothesis. These measures may act as effect modifiers or confounders for the primary explanatory variables. For a summary of the specific measures that are considered important for addressing Hypothesis 2.2, please see Tables 2.2a – 2.2g in Appendix B of this report.

Hypothesis 2.3 of the National Children's Study tests whether infection and mediators of inflammation during pregnancy and the perinatal period are associated with increased risk of schizophrenia. This hypothesis will be supported through psychological and neurological testing as well as through direct observation of schizophrenia in NCS index children at regular intervals throughout the study. School performance and related measures might be early indicators identifying children with schizophrenia, but these are not direct measures of risk or outcome. Because schizophrenia is generally not diagnosed until the late teens or early twenties, response and retention rates of NCS participants will be important for assessing this hypothesis. Based on statistics from Bresnahan et al. (2000), we can expect to observe schizophrenia among older teens and adults in approximately 1.0% of the study population.

Similar to Hypotheses 1.2 and 2.2, the primary explanatory variables that address this hypothesis are infection and mediators of inflammation during pregnancy and the perinatal period. These variables will be assessed by measures of maternal hormones and antibodies in venous blood samples collected from the mother during pregnancy and at birth, and by measures of cytokines in swab samples collected from the mother during pregnancy.

In addition to the primary response variables, there are a variety of covariates and potential confounders that are important to assess in support of Hypothesis 2.3. These may include such factors as economic status, race/ethnicity, and family history of mental illness, as well as genetic polymorphisms and mother's medicine usage during pregnancy. Fetal ultrasound performed during the second or third trimester of pregnancy might reveal the presence of any genetic polymorphisms. For a summary of the specific measures that are considered important for addressing Hypothesis 2.3, please see Tables 2.3a – 2.3g in Appendix B of this report.

Hypotheses 3.1 and 3.2 both focus on risk of injury as a primary outcome variable. These hypotheses were recently eliminated by the ICC but are currently being further evaluated and possibly strengthened for consideration as NCS hypotheses. The type and severity of injury that will be studied under these hypotheses are not fully specified at present. However, it is reasonable to assume that Hypotheses 3.1 and 3.2 will be supported via direct observation of an injury (or a history of repeated injuries) to the index child or through questionnaire, interview of the primary caregiver (or index child in later stages of life), or medical record review. Assessment of injury would likely occur at regular intervals throughout the performance of the NCS (e.g., every three months), with various different types of information being collected with respect to each injury event (e.g. type of injury, severity of injury, cause of injury, where the injury took place, presence of appropriate supervision, etc.). The CDC (2003) reports that, on average, about 10% of children across age groups are at increased risk of injury. Because these two hypotheses will be supported by ongoing data collection events, the response and retention rates of subjects included in the NCS will be an important issue.

Additional measures that may be important in assessing Hypotheses 3.1 and 3.2 include: socio-economic status, risk factors for injury in the child's residential environment and other micro-environments where the child spends time, quality of supervision, and assessment of risk-taking behavior in the index child. These measures may act as effect modifiers or confounders for the main explanatory variables. For a summary of the specific measures that are considered important for addressing Hypotheses 3.1 and 3.2, please see Tables 3.1a – 3.2g in Appendix B of this report.

Hypothesis 3.1 of the National Children's Study focuses on exposures early in life that lead to neurotoxic effects and their association with increased risk of injury. Exposures early in life that lead to neurotoxic effects comprise the main explanatory factors for Hypothesis 3.1. One complicating factor is that some of these hypothesized exposures (such as pesticide exposure) are themselves the subject of evaluation in this study. Therefore specification of the exact exposures of focus for this hypothesis will require the judgment of the study leaders. Another complicating factor is that, presumably, exposure early in life leading to neurotoxic effects could result from exposures that the biological mother faces prior to conception. For example, it is well known that maternal lead exposure prior to conception can have a strong impact on the blood-lead concentration of children. Lead is a strong neurotoxin that is linked to a variety of adverse health outcomes, including loss of IQ and motor functioning that could influence injuries later in life. However, estimates of preconception exposure may be able to be made from post-conception samples, e.g. blood- or bone-lead measurements collected post-conception.

To address the main explanatory factors for Hypothesis 3.1, we must first inventory the different types of chemical exposures that are of interest to determine how best to measure them among the NCS cohort with limited resources. For example, there are many exposures that have neurotoxic effects that are categorized as persistent bioaccumulative toxins that could be measured in blood samples of the index child at regular intervals. These persistent bioaccumulative toxins include lead, mercury, PCBs and many other persistent pesticides and chemical exposures of interest. There are other chemicals that are less persistent or non-persistent that also may have strong neurotoxic effects, such as organophosphate pesticides, prescription medications, over the counter medications, illegal drugs, alcohol and nicotine. As discussed in the text supporting Hypothesis 2.1, these chemicals may be more challenging for assessment as part of the NCS because traces of exposure are not likely to be as easy to assess (the exposures may be short-lived and not traceable through physical or biological sampling unless timed perfectly) while the subtle neurotoxic effects may be long-lasting. For these non-persistent neurotoxic chemicals, the NCS may require some surrogate measures. For example, questionnaires could be used to monitor activities, diet, and consumer product usage related to exposure to these chemicals. An aggregate exposure study performed on a limited size sub-sample of NCS participants (Strauss, et al, 2003) could be used to establish relationships between these surrogate measures of exposure and more direct measures of exposure for use in addressing this hypothesis.

Hypothesis 3.2 of the National Children's Study focuses on attributes of childcare and how a child's relationship with caregivers relates to risk of injury. Behavioral attributes of childcare and the child's relationship with caregivers are the main explanatory variables for Hypothesis 3.2. These may be assessed by social function measures obtained through interviews with the primary caregivers of the index child (e.g., mother, father, day care providers, teachers).

Hypothesis 3.3 of the National Children's Study studies the cumulative adverse effect of repeated head trauma on neurocognitive development. At this time, the type and severity of head trauma that will be studied under this hypothesis are not fully specified. However, it is anticipated that Hypothesis 3.3 will be supported by a range of behavioral, neurological, and developmental outcomes assessed via interviews, school records, and medical records. While the exact behavioral and neurological variables and the schedule for measuring them have not been determined, it is expected that measures of school performance and neurocognitive development will be collected throughout the conduct of the NCS study.

The primary explanatory variable is repeated head trauma. Occurrences of traumatic head injury may be determined through direct review of medical records and interviews with a responsible adult (parent or primary caregiver during early lifestages, or index child at later lifestages). Regular and continued assessment of traumatic head injury throughout the child's lifestages will be important to support this hypothesis. Data collection at regular intervals throughout the duration of the NCS (e.g., every three months) is recommended, with various types of information collected with respect to each injury event (e.g., type of injury, severity of injury, cause of injury, where the injury took place, whether appropriate supervision was present).

According to the CDC (1999), 7 of every 1000 children under the age of ten visit the emergency room for head trauma each year. Children with repeated head trauma would be expected to be less prevalent in this study in any given year – however there will be opportunity to aggregate the subset of the study population with repeated head trauma events over the course of the study. Because this hypothesis will be assessed through ongoing data collection from NCS subjects throughout the study, response and retention rates of NCS participants will be important. To reduce the burden of collecting injury data from NCS subjects at regular intervals, telephone interviews may be used.

Additional measures that may be important in assessing this hypothesis include: socio-economic status, risk factors for injury in the child's residential environment and other micro-environments where the child spends time, quality of supervision, and assessment of risk-taking behavior in the index child. These measures may act as effect modifiers or confounders for the main explanatory variables. For a summary of the specific measures that are considered important for addressing Hypothesis 3.3, please see Tables 3.3a – 3.3g in Appendix B of this report.

Hypotheses 4.1 through 4.6 represent a set of related research hypotheses that focus on a wide range of factors that might be associated with the outcome of increased or decreased risk of asthma. The CDC (2003) reports that, on average, asthma affects about 6% of children between the ages of 5 and 14. Therefore it may be possible to reduce expensive measures, primarily those associated with measuring exposure, by strategies that involve collecting certain measures on only a sample of the participants. On the other hand, because asthma is particularly difficult to diagnose in children under 5 years of age, it will be important that the study retain strong retention rates to address this set of hypotheses sufficiently.

Characterization of the outcome of asthma will likely require multiple measures, ranging from precursors of symptoms such as allergic sensitization, to symptoms, to effects such as medication use and doctor or hospital visits, to diagnoses methods that assess pulmonary function and airway reactivity. Data to support the outcome variables for this set of hypotheses will be collected through physical examinations, review of medical records, and interviews. Asthma symptom surveys completed approximately annually (by the primary caregiver during early childhood, or by the index child in later lifestages) are important outcome variables. Allergic skin tests conducted on the index child are recommended every year in the first three years and less frequently in later years. Other tests (e.g., exhaled gases, airway reactivity to bronchoprovocation in older children) could also be conducted on the index child at longer intervals (e.g., every three to five years) or only in older children, as appropriate. These include measures of immune system function (e.g., lymphocytes, cytokines, IgE, interleukins) and a DNA sample. Measures of immune system function would be assessed in the blood of the index child at convenient intervals during childhood and adolescence (e.g., at regular doctor office visits). Due to the relatively high prevalence of asthma, investigators may be able to reduce cost and increase the efficiency of collecting data from blood samples by choosing a sub-sample of index children to undergo testing after the age of 2 years. Outcome measures assessed by interview include: parents' history of allergy, asthma, and respiratory illness; and the index child's history of asthma, respiratory illness, and wheezing. This set of hypotheses would also be supported by observation of the index child's chest auscultation and pulmonary function at various lifestages and, upon death, by autopsy data.

Specific hypothesized exposure or risk factors are discussed below as they are identified for each hypothesis. In addition to the primary factors covered by Hypotheses 4.1-4.5, there are other risk factors that are very important to measure. These start with genetic susceptibility. Appropriate measures include measures of parents' history of allergy, asthma, and respiratory illness; family immune history; immune system function (e.g., lymphocytes, cytokines, IgE, interleukins), allergic skin tests, and a DNA sample.

In the case of asthma, while six separate hypotheses have been proposed, these cannot be considered independently because of the wide range of risk factors and interaction between risk factors that are associated with asthma. Therefore, the main explanatory variable for one hypothesis might be a critical covariate in another. This relationship should be kept in mind when reading the following summary explanations for Hypotheses 4.1 through 4.6. Other potential co-variates and confounders that may be important to assess in addressing these hypotheses include: race/ethnicity; economic status; size and composition of the immediate family; residential history; access to health care; and whether the index child was breastfed. The use of a vacuum with filter and the presence of a pet (with fur) are also strong predictors of asthma sensitization and exacerbation. The presence of lymphocytes and markers for infection and inflammation in the blood of the index child are additional potential confounders that are important for this hypothesis. Because smoking can be a risk factor for asthma, it is recommended that levels of cotinine (a marker of smoking) in the urine of the index child be assessed several times in the child's first ten years and at least once for the primary caregiver. It may be possible to reduce the burden of collecting urine samples from all NCS subjects by analyzing the urine of a sub-sample of subjects and comparing cotinine levels with the interview results from the entire NCS cohort.

A summary of the specific measures that are considered important for addressing Hypotheses 4.1 through 4.6 are combined in Tables 4.0a – 4.0g in Appendix B of this report.

Hypothesis 4.1 of the National Children's Study assesses whether exposure to indoor and outdoor air pollution and bioaerosols (including allergens, endotoxin, and mold) is associated with increased risk of asthma. The primary explanatory variables for this hypothes – indoor and outdoor air pollution and bioareosols – raise a challenging measurement issue. Significant measurements that should be considered include outdoor air pollutants such as O_3, NO_2, SO_2, $PM_{2.5}$, PM_{10}, diesel exhaust; hazardous air pollutants including the thirty compounds identified by EPA as having highest impact on asthma and respiratory health; and clinically relevant allergens such as molds, pollens, dust mites, insect and rodent allergens, and pet secretions. Some of these will be more difficult to characterize than others. For example, fungal allergens, while possibly important for asthma sensitization, are difficult to measure. Given the cost and burden of environmental sampling for many of these pollutants and bioaerosols, the sampling and measurement strategy will likely have to include area air sampling, questionnaire information as surrogates for physical samples, and use of a validation subset of the sample as described for other hypotheses. Matrix sampling might also be considered to spread the burden so that not all samples are collected from each participant.

Hypothesis 4.2 of the National Children's Study assesses whether respiratory viral infection early in life is associated with increased risk of asthma. Children are susceptible to a number of viruses early in life that can comprise respiratory function, some of which may be prevented with vaccinations. Review of the index child's medical records would indicate the type of vaccinations given and whether any doctor-treated respiratory illnesses had occurred. Other evidence of respiratory viral infection in the first year of the index child's life could also be ascertained by physical exam and biological sampling during sick child doctor's office visits. Additionally, it will be important to understand, by all of these methods, the role of other viruses that produce non-respiratory illnesses, e.g., gastrointestinal, since the total virus burden will affect the child's antibody status and subsequent risk of disease.

Hypothesis 4.3 of the National Children's Study assesses whether maternal stress during pregnancy is associated with increased risk of asthma in the index child. Multiple measures of maternal stress during pregnancy will serve as the main explanatory variables for this hypothesis. For example, in addition to questionnaire information on maternal stress, cortisol will be an important marker for assessing system stress in both the mother and index child. Ideally, cortisol would be measured in blood samples collected from the mother during preconception and the second trimester of pregnancy and in the index child during pregnancy by amniocentesis in the second trimester and at birth. The high burden of amniocentesis may have a significant impact on the NCS sampling design, as the procedure is invasive and carries a slight risk of miscarriage. Periodic cytokine swabs, perhaps every few years, for the index child are also of high importance as an explanatory variable. Cytokines can also be measured periodically in the blood of the index child. Experts in the interpretation of cytokine data will be called on to determine if two testing methods are indeed necessary.

Hypothesis 4.4 of the National Children's Study focuses on the relationship between antioxidant constituents of diet and decreased risk of asthma. The primary explanatory variables for Hypothesis 4.4 are measures of diet and nutrition from the mother, index child, and daycare provider, as a surrogate for the index child's diet in early childhood. Selenium, vitamin C, vitamin E (plus carotenoids), and N-3 and N-6 fatty acids are important antioxidants that will be assessed in the mother and child. Urine isoprostanes are markers of oxidant stress. Assessment of these measures can involve personal interviews, tests of oxidative stress response, and collection of blood and urine samples and exhaled breath condensates. Data collection could be obtained from the mother during pregnancy at routine prenatal visits and at birth through the cooperation of hospital or medical care providers; from the index child at well-baby visits in the first three years; and from the daycare provider in conjunction with the collection of data for other hypotheses.

Hypothesis 4.5 of the National Children's Study assesses whether early exposure to bacterial and microbial products decreases the risk of asthma (the hygiene hypothesis). The primary explanatory variables for Hypothesis 4.5 will be a variety of measures of exposure to bacterial and microbial products. In infancy, the index child can be examined for bacteroides, bifidobacteris, clostridia, enterococci, and staphyloccocus aureus. The index child's use of antibiotics is a strong measure of infection history while vaccinations are indicators of the reduced risk of certain infections. The index child's use of antibiotics, type of vaccinations given, as well as the mother's use of antibiotics prenatally, could be determined by review of medical records. Certain other measures, such as Type I diabetes diagnosis, atopic dermatitis history, and appropriate genetic markers may also be useful in determining a child's response to bacterial and microbial exposures, since some of these conditions may place the child at excess risk. Surrogate measures such as neighborhood conditions, and exposures to farm and domestic animals, will also likely be of interest.

Hypothesis 4.6 of the National Children's Study focuses on access to health care and management of asthma and the relationship to asthma hospitalization. The primary outcome of interest for Hypothesis 4.6 – hospitalization – will be assessed by number of hospitalizations, trips to the emergency room, physician office visits, and health insurance claims. This information would be obtained through review of medical records and interviews with a responsible adult beginning at birth and continuing throughout the life of the index child at frequent intervals. Asthma symptom surveys completed approximately annually (by the primary caregiver during early childhood, or by the index child in later lifestages) would also useful. The primary explanatory variables for hospitalization due to asthma are access to health care and management of asthma. Measures with which to assess these variables include: characteristics of the neighborhood in which the family lives, socio-economic status, social function, amount and type of health care insurance, and use of the health care system. These measures can be obtained via review of medical records and interview with a responsible adult of the household beginning at preconception and continuing through birth, childhood, adolescence, and adulthood at periodic intervals.

Additional measures that may be important in assessing this hypothesis include: the primary caregiver's knowledge of health care options and asthma management techniques, the family's residential history, occupational history and the content and quality of health care. These measures may act as effect modifiers or confounders for the main explanatory variables. The specific measures that are considered important for addressing Hypothesis 4.6 are similar to those for Hypotheses 4.1 through 4.5 and are combined in Tables 4.0a – 4.0g in Appendix B of this report.

Hypotheses 5.1 through 5.6 are a set of similar hypotheses that focus on the risk of obesity and insulin resistance as the primary outcome variables. Body size, blood pressure, serum insulin levels, and measures of growth hormone in the index child would be used to measure the outcome variables at periodic physical exams throughout the NCS study (e.g., every five years). The frequency of these exams could be altered to coincide with well-child office visits or school-related physicals. The analysis of blood levels of serum insulin and growth hormone during childhood and adolescence could possibly coincide with blood sampling for other hypotheses. Body mass indices and genetic markers of obesity in the mother and father are important for this set of hypotheses, though the latter may be difficult to obtain. Physical activity and its direct or indirect relationship to obesity will be evaluated through, among other measures, time activity patterns of the index child observed at frequent intervals during the course of the NCS study. According to Mokad et al. (1999) obesity is prevalent in approximately 15.3% of children aged 6-11 and 15.5% of children aged 12-19. Brand-Miller et al. (2002) reports that insulin resistance may be as high as 25% in the overweight population. Taken together, these data support the suggestion that the prevalence of obesity and obesity-related illnesses may allow the use of sampling to reduce the number of measures taken for each participant.

In addition to the primary response variables, a variety of potential co-variates and confounders may be important to assess in addressing Hypotheses 5.1 through 5.6. These include: cultural norms, socio-economic status, education, medical history of the index child, family history of diabetes and obesity, lifestyle factors, values with respect to diet, and other factors related to the risk of obesity.

Note that the main explanatory variable for one hypothesis may be a co-variate for another hypothesis within this set. This relationship should be kept in mind when reading the following summary explanations for Hypotheses 5.1 through 5.6. A summary of the specific measures that are considered important for addressing each hypothesis can be found in Tables 5.0a – 5.0g in Appendix B of this report.

Hypothesis 5.1 of the National Children's Study focuses on the relationship between impaired maternal glucose metabolism during pregnancy and the risk of obesity and insulin resistance in offspring. The main explanatory variable for Hypothesis 5.1—impaired maternal glucose metabolism (see also Hypothesis 1.1)—must be assessed during pregnancy. Impaired glucose metabolism during pregnancy can be assessed using multiple measures from venous samples of blood collected from the mother during routine prenatal visits. These measures include glucose tolerance, blood glucose concentration, and serum insulin concentration. It will be important to understand how measures of impaired glucose metabolism are likely to vary over the course of pregnancy (e.g., by measuring each trimester). While a validation study could be used to reduce the number of blood samples collected from the main NCS cohort for this hypothesis, blood samples collected in support of other hypotheses could be utilized for this hypothesis as well. The extent to which measures of impaired glucose metabolism can be assessed from stored or archived samples of blood may provide other avenues of efficiency through the use of outcome dependent sampling from within the NCS cohort. This might entail the conduct of a matched case/control study from within the NCS cohort in which a much smaller and efficient sample of children with and without evidence of obesity or insulin resistance be used to address this hypothesis.

In addition to the direct measures of impaired glucose metabolism, there are other measures from blood samples collected during pregnancy that may be important in assessing this hypothesis, including HgbA1C, lipid profile, glucokinase mutation, and hormone levels such as cortisol. These additional measures may act as effect modifiers or confounders for the main explanatory variable.

Hypothesis 5.2 of the National Children's Study addresses the relationship between intrauterine growth restriction, as determined by serial ultrasound examination, and subsequent risk of central (i.e., mid-body) obesity and insulin resistance in offspring, independent of body mass. The main explanatory variable for Hypothesis 5.2—intrauterine growth restriction—must be assessed during pregnancy. Intrauterine growth restriction can be assessed during pregnancy by serial ultrasounds (at least two) of the fetus performed in the second and third trimesters. While one ultrasound may be included as part of routine prenatal care, additional ultrasounds may introduce added cost, though probably not undue burden on the mother or fetus. A validation study that assesses the amount of temporal variability (daily, weekly, monthly) in intrauterine growth restriction among a small sample of pregnant women combined with the use of statistical methods that correct for measurement error in explanatory variables might allow investigators to reduce the need for multiple ultrasounds among the main NCS cohort to a single ultrasound performed during pregnancy to address this hypothesis.

Hypothesis 5.3 of the National Children's Study assesses whether breast milk feeding, compared with infant formula feeding, and breastfeeding duration are associated with lower rates of obesity and lower risk of insulin resistance. Breast milk feeding and duration, as the main explanatory variables for Hypothesis 5.3, will be assessed by interview at birth, at four well-baby visits in the index child's first year, and twice in year 2. Components of breast milk samples will be used as indicators of maternal diet, drug usage, and other relevant elements that can be passed on to the child.

Hypothesis 5.4 of the National Children's Study addresses whether dietary predictors of obesity and insulin resistance include reduced intake of fiber and whole grains, and a high glycemic index of the diet. Levels of glucose in the blood of the index child can measure glycemic index in infancy, childhood, and adolescence. A glycemic index of the diet may be constructed using a food intake diary or related questionnaire. The amount of fiber and whole grains in the diet of the index child would be assessed through regular interviews with a parent or primary caregiver in infancy and childhood, and with the index child in adolescence.

Hypothesis 5.5 of the National Children's Study focuses on environmental factors such as distance to parks, availability of walking routes in the neighborhood, and neighborhood safety in relationship to the risk of obesity and insulin resistance. The primary explanatory variables for this hypothesis include environmental factors that indicate opportunities for the index child to exercise. Such factors include distance to parks, availability of walking routes in the neighborhood, and neighborhood safety, as measured by the location of play areas in the neighborhood, neighborhood characteristics, residential environment (e.g., space to play, presence of a playset), and other indicators. These factors would be assessed by interview with a parent or primary caregiver in the prenatal period, childhood, and adolescence. There may also be assessment by visual inspection of the neighborhood, especially if the visual inspection would be useful to other hypotheses as well. Direct visual assessment by study personnel would also reduce burden on the participants.

Hypothesis 5.6 of the National Children's Study assesses whether social, behavioral, and family factors that affect development of dietary preferences and physical activity patterns early in childhood determine risk of childhood obesity and insulin resistance. Such factors include parents' knowledge of good diet habits, family's health-related quality of life, lifestyle, and parents' work schedules. These factors would be assessed by interview with a parent or primary caregiver in the prenatal period, childhood, and adolescence.

Hypothesis 5.7 of the National Children's Study assesses whether *in utero* and subsequent exposure to environmental agents that affect the endocrine system (e.g., bisphenol A, atrazine, and lead) results in altered age at puberty. The primary outcome for this hypothesis—age at puberty—can be measured by Tanner stage examinations, age at menarche (for girls), and presence of sperm in urine (for boys). The menstrual history of the index child (females) is another important outcome variable (in later lifestages). According to the CDC (2003), the average age of puberty for girls is between the ages of 8 and 13, and the average age of puberty for boys is between the ages of 9 and 14. Annual Tanner stage examinations of the index child beginning in pre-adolescence (years 6-7) and continuing through adolescence (years 8-18) are recommended. While the need for yearly examinations could be reduced, at least one examination should be performed during pre-adolescence and one during adolescence for the entire NCS cohort. These examinations could possibly coincide with well-child office visits or school-related physicals. It will be important to have strong retention rates in this study in order to address this hypothesis with sufficient power.

In utero and subsequent exposure to environmental agents that affect the endocrine system is the primary explanatory variable for Hypothesis 5.7. Exposure to environmental agents can be assessed by metabolite levels of bisphenol A and atrazine in the urine of the mother during pregnancy, at birth, and throughout the duration of nursing. Exposure to other environmental chemicals that may have the potential to affect endocrine function (e.g., lead, dioxins, PCBs) are important in assessing this hypothesis as well. Such chemicals would be measured in blood samples collected from the mother during pregnancy and nursing and from the index child throughout all lifestages beginning at birth. To maximize efficiency, blood samples collected for this hypothesis would be utilized for multiple hypotheses.

Urine cotinine measures throughout pregnancy and nursing are important as potential covariates. Other potential covariates and confounders that are important to assess in support of Hypothesis 5.7 include diet and nutrition measures, smoking status of parents, mother's menstrual and reproductive history, gestational age at birth, and mother's alcohol consumption during pregnancy. For a summary of the specific measures that are considered important for addressing Hypothesis 5.7, please see Tables 5.7a – 5.7g in Appendix B of this report.

II. CONCLUSIONS AND RECOMMENDATIONS

This report provides an initial assessment of likely measures and methods that can or will be used to address the current set of core hypotheses. Examination of the identified measures across hypotheses, especially those which are critical to testing the hypotheses, leads to a number of preliminary conclusions related to a) which required measures or groups of measures might be important in the selection of a sampling design option; and b) opportunities for burden reduction, cost savings, and efficiency across hypotheses.

MEASURES OR GROUPS OF MEASURES THAT ARE IMPORTANT TO SELECTION OF A SAMPLING DESIGN OPTION

Review of the measures leads to a number of observations:

1. Delivery room or birth samples such as placenta, umbilical cord cultures, and amniotic fluid, are critical measures for several hypotheses. Therefore these required measures favor design options that increase the likelihood or efficiency of collecting samples at birth, and obtaining the cooperation of obstetrical providers and hospitals.
2. A wide variety of prenatal samples will be required, including biological and physical measures, including measures, such as ultrasounds, that require the use of medical facilities. The impact of the extensive prenatal measurement requirements are far-reaching, and may be difficult to assess relative to different sampling design options. For example, selection of women independent of access or quality of prenatal care may be difficult under some designs, but biases may be introduced if the prenatal measurement requirements lead to recruitment only of women who have access to good prenatal care.
3. With the exception of Hypothesis 1.1, which addresses women "without diabetes before pregnancy," it appears that preconception measures are not critical to the core hypotheses. Even for Hypothesis 1.1, the case could be made that a self-reported medical diagnosis of diabetes pre-pregnancy collected retrospectively during pregnancy might be sufficient to address the hypothesis. Therefore, if design options are to be distinguished based on the ability to collect measures preconception, the case for this should probably be based on the NCS goal of serving as a resource for future studies, not on requirements for the core hypotheses.
4. The collection of environmental samples will most likely require sampling methods that can reduce the cost and burden of sampling. Potential methods for reducing the burden are discussed below. Impact on the sampling design options is possible. Two examples are a) if there are significant cost efficiencies associated with certain geographic areas (for example, if current air monitoring data can be used); or b) if certain subpopulations will increase the range of exposures or ability to collect samples. The specific implications on sampling design can be assessed after a more precise determination of the specific environmental samples that are to be collected.
5. While the majority of measures will be collected in the early life stages, the measures that are expected to be collected at later life stages significantly favor designs that maximize retention in the study.
6. The burden on study participants will be significant, with many ramifications. For one example, there may be an issue with the amount of blood required to allow analysis for all the measures required under the different hypotheses, especially at the early life stages. As another example, the recommended battery

of tests for assessing neurobehavioral and cognitive functions at different stages of development as part of the NCS are not yet fully developed and specified, and these tests are likely to be performed in a clinical setting and be time consuming and costly to implement. The burden will have an impact on recruitment and retention that may vary according to sampling design option.

OPPORTUNITIES FOR BURDEN REDUCTION, COST SAVINGS, AND EFFICIENCY ACROSS HYPOTHESES

While the number and variety of required measures is daunting in many aspects, it is also evident that the current set of hypotheses allows certain important flexibilities.

First, in most cases there appears to be reasonable flexibility in the timing of measures. There are few, if any, critical preconception measures, and many of the prenatal measures have flexibility in when they must be collected. This conclusion is based on an assumption that these measures can either be reasonably reconstructed using retrospective methods or that sophisticated statistical techniques can be used to adjust models for the relationship between an adverse health outcome and a mis-timed measure of exposure.

Second, there are multiple ways to reduce the burden and cost of data collection and increase efficiency when addressing the hypotheses. These include consolidation of data collection across hypotheses, collecting subsets of more detailed data from a sample of participants rather than all participants, postponing the choice of analysis of physical samples until a later date, and collecting more precise and burdensome measures on a small subset of participants while collecting less precise measures on the full cohort. While all of these options require difficult tradeoffs between cost, burden, and quantity or quality of information, they do provide the flexibility to conduct a study under the kind of cost and cohort burden constraints that will inevitably be imposed upon it.

Opportunities for Consolidation of Data Collection across Hypotheses

To the extent that the priority outcomes and core hypotheses for the NCS were developed independently of one another, there is inevitable overlap of proposed measurement. Indeed, this requirement to collect the same data for many hypotheses would have occurred even if they had been offered by a single group. To the extent that many of the data elements overlap, there is significant opportunity for the consolidation of data collection across hypotheses. One efficient way in which to accomplish this would be to develop a standard NCS Demographic Data Collection Form. For example, all hypotheses will require some demographic data, such as data from the parents regarding variables such as age, race/ethnicity, occupational data, residential history, income, educational status, etc.

The concept of consolidating data collection may also influence the way in which the NCS gathers more detailed information. For example, the NCS may only require detailed data about occupational exposures from those who undergo detailed exposure assessment chemical sampling. Similarly, many measurements from blood drawn at the same lifestages are required to test more than one hypothesis. Examples include serum glucose and insulin measure, lipid profiles, cytokines, and IgE. Again, these offer opportunities for consolidation of data collection, thus reducing both cost and subject burden.

Opportunities for Reducing the Amount of Data Collection or Chemical Analysis by Sampling

The health outcomes named in the hypotheses vary in level of occurrence, both incidence and prevalence. In a cohort of 100,000 children, as few as 200 children would likely be diagnosed with cerebral palsy, only 600 with congenital heart defects, and only 300 with autism. Many of the other outcomes, especially birth defects, have similarly small numbers. By contrast, over 6,000 children would be expected to be diagnosed with asthma by age 18. Where the numbers are sufficient, it may be feasible to test certain hypotheses with carefully drawn samples of the available population that meets the inclusion and exclusion criteria. Other opportunities will present themselves when the number of available subjects that meet specified criteria exceed the minimum sample size that has been calculated to test the hypothesis at the desired level of power. As other portions of this document indicate, there will probably be many opportunities to reduce the amount of chemical analysis of physical samples collected by sampling within the cohort. For example, a nested case-control study within the NCS cohort might be used to efficiently study rare health outcomes such as those discussed above. By using an outcome-dependent design and relying on archived blood, urine, and/or environmental samples, the NCS could experience large savings in the costs associated with chemical analysis of these samples.

Opportunities for Reducing the Burden of Data Collection by Collecting Less Precise Measures on the Majority of the Participants and More Precise Measures on a Small Validation Subset of the Participants

There are many instances in which questionnaire/interview data might be considered as a less expensive (and almost certainly less accurate) method of obtaining a direct measure of health status or exposure. For example, one of the hypotheses requires a measure of pre-pregnancy diabetes status as an exclusion criterion. This could be measured directly through preconception blood samples, or through a retrospective question on medical history (which may be both less costly, and less accurate). Similarly, exposure to tobacco smoke (ETS) may be ascertained via measures of cotinine in serum or urine, from a nicotine badge placed in the home, or through questionnaire/interview. The badge may be less accurate since it would detect only residential tobacco smoke exposure, while the questionnaire may miss some other exposures.

In the text supporting specific hypotheses, we provide examples of how less expensive methods could be used to obtain surrogate measures across the majority of the NCS cohort without necessarily compromising the ability to address the research objective. However, these choices must be considered carefully within the context of the integrated data collection protocol for NCS participants and the impact of lesser methods/measures on the acceptability of research results by the scientific community.

Related to the issue of the precision of measures and how it can be systematically accounted for in the design is the issue of self-reported data and their effect on validity. Many of the measurements proposed within the NCS will be reported by a parent, another adult familiar with the index child, or perhaps by a child who has become old enough to respond. It is proposed that both face-to-face interview methods and self-administered questionnaires be used for data collection. We recognize that self-reported data has limitations both with respect to reliability and validity, whether the result of poor memory, misunderstanding of the question, or reluctance to share personal information. Some measurements may be more prone to these problems than others. For example, variables such as smoking and alcohol consumption tend to be routinely under-reported. Surveys of diet and nutrition can be inaccurate because of memory issues and the inability to estimate food serving sizes. To address some of these concerns, we offer some recommendations to measure and perhaps increase the validity of the data obtained. For example, there are many measurements that are amenable to collection either by interview or self-completed questionnaire. One option would be to split the sample, interview some respondents, and let others fill out a questionnaire. To the extent that the samples are believed to be comparable with respect to the variables under consideration, the degree of discrepancy between the two methods might be an indicator of validity. Another option would be to take a small sample of families, interview one parent, give the other a questionnaire, and determine the degree of consistency in their answers. With regard to dietary histories, many methods have been proposed to increase validity, including diaries, obtaining information independently from more than one household member, showing food samples, and others. The most appropriate format generally depends on whether the greater interest is in recent or in long term, even lifetime, diet. As the protocols for the NCS are developed, careful consideration should be given to the methods used for self-reported data (both self-administered questionnaires and NCS-conducted interviews), including the use of pilot studies to assess reliability and validity.

Table 1.0. Summary of Outcome and Explanatory Variables (Incidence or Prevalence where Available), Methods and Measures, Lifestages, Covariates for NCS Hypotheses

Hypoth-esis	Outcome Variables					Explanatory Variables					
	Primary Outcome Variables	**Incidence or Prevalence of Outcomes**	**Methods**	**Measures**	**Life Stages**	**Primary Explanatory Variables**	**Incidence or Prevalence of Risk Factors**	**Methods**	**Measures**	**Life Stages**	**Example Covariates, Confounders, Effect Modifiers**
1.1	Major congenital malforma-tions of the heart, central nervous system, and all birth defects combined	Congenital heart defects: 0.60%; CNS defects: 0.60%; All birth defects: about 3.00%	Direct Observation by Medical Professional	Any birth defects	Birth through Adolescence	Impaired glucose metabolism during pregnancy		Blood	Glucose Tolerance, Blood Glucose and Serum insulin levels	1st, 2nd, 3rd Trimes-ters	Family history, mother's medical history
1.2	Preterm birth	Approximately 2% preterm births	Direct Observation by Medical Professional	Gestation <37 weeks	Birth	Intrauterine exposure to mediators of inflammation due to infection	2% intra-uterine infection	Interview, Blood, Swabs	Cytokines, WBC, Antibodies	1st, 2nd, 3rd Trimes-ters	Mother's medical history, recent infections
2.1	Neurobeha-vioral and cognitive effects during infancy and childhood	Uncertain	Neuro & Psych Testing	Abnormal neuro and cognitive results	Infancy through Year 21	Repeated low level exposures to nonpersistent pesticides *in utero* or postnatal	Plasma of 1% pregnant women reveals OP exposures	Blood, Urine, Env Air and Dust Sampling	Mother's pesticide levels; environ-mental levels	1st, 2nd, 3rd Trimes-ters through Year 7	Mother's medicine usage, occupational history, diet and nutrition; child's residential environment

Table 1.0. Summary of Outcome and Explanatory Variables (Incidence or Prevalence where Available), Methods and Measures, Lifestages, Covariates for NCS Hypotheses

	Outcome Variables					Explanatory Variables					
Hypoth-esis	**Primary Outcome Variables**	**Incidence or Prevalence of Outcomes**	**Methods**	**Measures**	**Life Stages**	**Primary Explanatory Variables**	**Incidence or Prevalence of Risk Factors**	**Methods**	**Measures**	**Life Stages**	**Example Covariates, Confounders, Effect Modifiers**
2.2	Neurode-velopmen-tal disabilities, e.g., CP, autism	CP: 0.20%; Autism by age 3: 0.30%	Cord blood; Neuro & Physical Exams	Abnormal findings on autism screening test; umbilical cord pathology	Infancy through Year 7	Prenatal Infection and mediators of inflammation		Blood, Swabs, Obstetric Med Hx	Vaginal & cervical cultures, interleukins, infection serology	Preg-nancy	Mother's medical and obstetric history, family history
2.3	Schizo-phrenia	Schizophrenia: 1.00% (older teens and adults	Neuro & Psych Testing; Direct Observat ion	Neuro & Psych Testing Results	Infancy through Year 21	Infection and mediators of inflammation during pregnancy and perinatal period		Interview, Blood, Swabs	Maternal hormones, cytokines	1st, 2nd, 3rd Trimes-ters, at birth	Family history, economic status, genetic polymorphisms, mother's medicine usage
3.1*	Increased Risk of Injury	Ave about 10% across age groups	Interview , Medical Record Review	Injury events	Every three months, Infancy through Year 21	Exposures to neurotoxins, e.g., PCB, mercury, Pb, pesticides, other metals		Blood, Interview, Env. Air and Dust	PCB, mercury, Pb, pesticides, other metals	Birth through Year 5	Occupational history, diet and nutrition; child's residential environment
3.2*	Increased Risk of Injury	Ave about 10% across age groups	Interview , Medical Record Review	Injury events	Every three months, Infancy through Year 21	Behavioral attributes of childcare; relationship with caregivers		Interviews	Social function measures	Birth through Adolesce nce	SES, residential environment

Table 1.0. Summary of Outcome and Explanatory Variables (Incidence or Prevalence where Available), Methods and Measures, Lifestages, Covariates for NCS Hypotheses

Hypoth-esis	Outcome Variables					Explanatory Variables					
	Primary Outcome Variables	**Incidence or Prevalence of Outcomes**	**Methods**	**Measures**	**Life Stages**	**Primary Explanatory Variables**	**Incidence or Prevalence of Risk Factors**	**Methods**	**Measures**	**Life Stages**	**Example Covariates, Confounders, Effect Modifiers**
3.3	Neurocog-nitive develop-ment		Inter-views, school records, medical records	Behavioral, neuro, and develop-mental outcomes	Infancy through Year 21	Repeated head trauma	7/1000 children <10 years have ER visit for head trauma	Interview; Medical records	Traumatic brain injury	Every 3 months	SES, residential environment
4.1	Increased Risk of Asthma	Asthma 5-14 years: 6.00%	Physical Exam, Medical Record Review	Allergy, asthma in index child, airway reactivity	Year 1 through year 21	Indoor and outdoor air pollution, bioaerosols, inc allergens, endotoxin, mold		Env air and dust samples, interviews	Diesel exhaust, NO_2 , allergens, mold	Year 1 through year 21	Infections, inflammations, lymphocytes, urine cotinine, smoking, health care access
4.2	Increased Risk of Asthma	Asthma 5-14 years: 6.00%	Physical Exam, Medical Record Review	Allergy, asthma in index child, airway reactivity	Year 1 through year 21	Respiratory viral infection		Medical histories, Physical Exams	lympho-cytes, cytokines markers	Birth through Year 5	Smoking, family lifestyle factors, health care access
4.3	Increased Risk of Asthma	Asthma 5-14 years: 6.00%	Physical Exam, Medical Record Review	Allergy, asthma in index child, airway reactivity	Year 1 through year 21	Maternal stress during pregnancy		Interview, Blood	Mother's alcohol consump-tion, smoking, psychoso-cial stress, Cortisol	Preconce ption, 1st, 2nd, 3rd trimes-ters	Lifestyle factors, occupational history, mother's history of allergy and asthma

Table 1.0. Summary of Outcome and Explanatory Variables (Incidence or Prevalence where Available), Methods and Measures, Lifestages, Covariates for NCS Hypotheses

Hypoth-esis	Outcome Variables					Explanatory Variables					
	Primary Outcome Variables	**Incidence or Prevalence of Outcomes**	**Methods**	**Measures**	**Life Stages**	**Primary Explanatory Variables**	**Incidence or Prevalence of Risk Factors**	**Methods**	**Measures**	**Life Stages**	**Example Covariates, Confounders, Effect Modifiers**
4.4	Decreased Risk of Asthma	Asthma 5-14 years: 6.00%	Physical Exam, Medical Record Review	Allergy, asthma in index child, airway reactivity	Year 1 through year 21	Antioxidant constituents of diet in mother, other adults, and index child		Diet and Nutrition Measures , exhaled breath conden-sate	Vitamin C, Vitamin E, , fatty-acid markers	Birth through year 21	Smoking, psychological history, history of infections in index child, allergic sensitization in index child
4.5	Decreased Risk of Asthma	Asthma 5-14 years: 6.00%	Physical Exam, Medical Record Review	Allergy, asthma in index child, airway reactivity	Year 1 through year 21	Exposure to bacterial and microbial products		Medical history, blood, dietary measures	air survey, bacteria and other infection measures	Birth through Year 5	Smoking, psychological history, history of infections in index child, allergic sensitization in index child, medicine usage in index child
4.6	Asthma Hospitaliza-tion	Asthma 5-14 years: 6.00%	Medical Record Review, Interview	Health Insurance claims, Hospital visits	Year 1 through year 21	Access to health care and management of asthma		Interview; Medical records	Neighborho od charac-teristics; health insurance; social function; SES; health care usage	Birth through year 21	Health-related knowledge; residential history; occupational history; content and quality of health care;

Table 1.0. Summary of Outcome and Explanatory Variables (Incidence or Prevalence where Available), Methods and Measures, Lifestages, Covariates for NCS Hypotheses

Hypoth-esis	Outcome Variables					Explanatory Variables					
	Primary Outcome Variables	Incidence or Prevalence of Outcomes	Methods	Measures	Life Stages	Primary Explanatory Variables	Incidence or Prevalence of Risk Factors	Methods	Measures	Life Stages	Example Covariates, Confounders, Effect Modifiers
5.1	Risk of Obesity and Insulin Resistance in Offspring	Obesity: 15.30% ages 6-11; 15.50% ages 12-19; Insulin resistance may be as high as 25.00%	Medical Record Review, Physical Exam, Blood	Body size; serum insulin levels; blood pressure; growth hormones	Year 1 through year 21	Impaired glucose metabolism during pregnancy		Blood	Glucose Tolerance, Blood Glucose and Serum insulin levels	1st, 2nd, 3rd trimes-ters	Family history of obesity and diabetes; lifestyle factors
5.2	Risk of central obesity and insulin resistance, independen t of BMI	Obesity: 15.30% ages 6-11; 15.50% ages 12-19; Insulin resistance may be as high as 25.00%	Medical Record Review, Physical exam; Blood	Abdominal girth; serum insulin levels, blood pressure	Year 1 through year 21	Intrauterine growth restriction		Ultra-sound	Fetal ultrasound	1st, 2nd, 3rd trimester	Diet and nutrition, physical activity, medical history of index child
5.3	Lower rates of obesity and lower risk of insulin resistance	Obesity: 15.30% ages 6-11; 15.50% ages 12-19; Insulin resistance may be as high as 25.00%	Medical Record Review, Physical Exam, Blood	Body size; serum insulin levels; blood pressure; growth hormones	Year 1 through year 21	Breast milk feeding and duration		Interview; Sample Breast Milk	Frequency and amount of feeding	Birth through Year 2	Physical activity, medical history of index child, family medical history

Table 1.0. Summary of Outcome and Explanatory Variables (Incidence or Prevalence where Available), Methods and Measures, Lifestages, Covariates for NCS Hypotheses

Hypoth-esis	Outcome Variables					Explanatory Variables					
	Primary Outcome Variables	**Incidence or Prevalence of Outcomes**	**Methods**	**Measures**	**Life Stages**	**Primary Explanatory Variables**	**Incidence or Prevalence of Risk Factors**	**Methods**	**Measures**	**Life Stages**	**Example Covariates, Confounders, Effect Modifiers**
5.4	Obesity and insulin resistance	Obesity: 15.30% ages 6-11; 15.50% ages 12-19; Insulin resistance may be as high as 25.00%	Medical Record Review, Physical Exam, Blood	Body size; serum insulin levels; blood pressure; growth hormones	Year 1 through year 21	Reduced intake of fiber and whole grains, and high glycemic index		Interview	Diet and nutrition measures	Year 1 Through Year 21	Family history of obesity and diabetes; lifestyle factors; physical activity
5.5	Risk of Obesity and Insulin Resistance in Offspring	Obesity: 15.30% ages 6-11; 15.50% ages 12-19; Insulin resistance may be as high as 25.00%	Medical Record Review, Physical Exam, Blood	Body size; serum insulin levels; blood pressure; growth hormones	Year 1 through year 21	Environmental factors such as distance to parks, availability of walking routes, neighborhood safety		Interview	Residential environ-ment; demograph-ic data, lifestyle factors, physical activity, cultural norms,	Year 1 Through Year 21	Cultural norms, residential environment, values wrt diet, social function

Table 1.0. Summary of Outcome and Explanatory Variables (Incidence or Prevalence where Available), Methods and Measures, Lifestages, Covariates for NCS Hypotheses

	Outcome Variables					Explanatory Variables					
Hypoth-esis	**Primary Outcome Variables**	**Incidence or Prevalence of Outcomes**	**Methods**	**Measures**	**Life Stages**	**Primary Explanatory Variables**	**Incidence or Prevalence of Risk Factors**	**Methods**	**Measures**	**Life Stages**	**Example Covariates, Confounders, Effect Modifiers**
5.6	Risk of Obesity and Insulin Resistance in Offspring	Obesity: 15.30% ages 6-11; 15.50% ages 12-19; Insulin resistance may be as high as 25.00%	Medical Record Review, Physical Exam, Blood	Body size; serum insulin levels; blood pressure; growth hormones	Year 1 through year 21	Social, behavioral, family factors that affect dietary preferences and physical activity patterns		Interview	Health-related social, behavioral, factors	Year 1 Through Year 21	Smoking, SES, transportation methods, neighborhood characteristics
5.7	Altered age at puberty	Ave for girls: 8-13 years; Ave for boys: 9-14 years	Physical exam; urine	Tanner stages; age at menarche; presence of sperm in urine	Through Puberty	*In utero* and subsequent exposure to environmental agents that affect endocrine system		Blood, Urine, Interview	Metabolites levels of bisphenol A and atrazine	Prenatal Through Year 9	Lifestyle factors, smoking, medicine usage, exposure to environmental chemicals; mother's reproductive history

* Hypotheses 3.1 and 3.2 were recently eliminated by the ICC but are currently being further evaluated and possibly strengthened for consideration as NCS hypotheses.

Table 2.0 Measurement Methods and Timeline for Sampling for Hypotheses†

All Participants

(M = Mother; F = Biological Father; C = Index Child; A = Other Adult)

*** = Preconception measure would be preferable, if available.**

	Priority Outcome	Pregnancy Outcomes		Neurobehavorial Development			Injury			Asthma						Obesity and Altered Physical Development						
Lifestage	**Method**	**1.1**	**1.2**	**2.1**	**2.2**	**2.3**	**3.1****	**3.2****	**3.3**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**
Preconception (If Available)	Blood	M*	M*	M*			M*															M*
	Urine			M*			M*															
	Other Physical Sampling		M*																			
	Medical Record Review																					
	Interview/ Questionnaire																					M*
	Direct Observation	M*																				
1st Trimester (or Upon Enrollment)	Blood	MF	M	MF	M	M	M			MF	MF	MF	MF	MF	MF	MF	MF			MF	MF	M
	Urine			M			M*			M	M	M	M	M	M							M
	Other Physical Sampling		M		M	MF																
	Medical Record Review	MF	M				M										M					
	Interview/ Questionnaire	MF	M	MF		MF	MF			MF	MF	MF	MF	MF	MF	MF		M		MF	MF	MF
	Direct Observation	M	M													M		MF	MF	MF		M

Table 2.0 Measurement Methods and Timeline for Sampling for Hypotheses†

All Participants

(M = Mother; F = Biological Father; C = Index Child; A = Other Adult) *** = Preconception measure would be preferable, if available.**

	Priority Outcome	Pregnancy Outcomes		Neurobehavorial Development			Injury			Asthma						Obesity and Altered Physical Development						
Lifestage	**Method**	**1.1**	**1.2**	**2.1**	**2.2**	**2.3**	**3.1****	**3.2****	**3.3**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**
2nd Trimester	Blood	M	M	M	M	M	M			MF	MF	MF	MF	MF	MF	M	M				M	M
	Urine			M			M*			M	M	M	M	M	M							M
	Other Physical Sampling		M		M	M																
	Medical Record Review		M				M										M					
	Interview/ Questionnaire	M	M	M		M	M			MF	MF	MF	MF	MF	MF	M	MF					M
	Direct Observation	M	M		C	C										M	M					M
3rd Trimester	Blood	M		M	M	M	M			MF	MF	MF	MF	MF	MF	M	M				M	M
	Urine			M			M*			M	M	M	M	M	M							M
	Other Physical Sampling		M		M	M																
	Medical Record Review		M														M					
	Interview/ Questionnaire	M	M	M		M	M			MF	MF	MF	MF	MF	MF	M	M					M
	Direct Observation	M	M		C	C										M	M					M

Table 2.0 Measurement Methods and Timeline for Sampling for Hypotheses[†]

All Participants

(M = Mother; F = Biological Father; C = Index Child; A = Other Adult) *** = Preconception measure would be preferable, if available.**

	Priority Outcome	Pregnancy Outcomes		Neurobehavorial Development			Injury			Asthma						Obesity and Altered Physical Development						
Lifestage	**Method**	**1.1**	**1.2**	**2.1**	**2.2**	**2.3**	**3.1****	**3.2****	**3.3**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**
Birth	Blood		M	MC	M	M				MF	MF	MF	MF	MF	MF		M				M	M
	Urine																					
	Other Physical Sampling		C	M	MC	MC				M	M	M	M	M	M			M				
	Medical Record Review	C				M																
	Interview/ Questionnaire							MFA	MFA	MF	MF	MF	MF	MF	MF		M					MF
	Direct Observation	C	C	C		C			C								C	C				M
Y1 -1 (0-3 months)	Blood									C	C	C	C	C	C			C				M
	Urine																					
	Other Physical Sampling			M													M	MC				
	Medical Record Review																					
	Interview/ Questionnaire			C													M	MC				M
	Direct Observation	C							C	C	C	C	C	C	C							

Table 2.0 Measurement Methods and Timeline for Sampling for Hypotheses†

All Participants

(M = Mother; F = Biological Father; C = Index Child; A = Other Adult) *** = Preconception measure would be preferable, if available.**

	Priority Outcome	Pregnancy Outcomes		Neurobehavorial Development			Injury			Asthma						Obesity and Altered Physical Development						
Lifestage	**Method**	**1.1**	**1.2**	**2.1**	**2.2**	**2.3**	**3.1****	**3.2****	**3.3**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**
Y1-2 (4-6 months)	Blood									C	C	C	C	C	C							
	Urine																					
	Other Physical Sampling			M													M					
	Medical Record Review																	M				
	Interview/ Questionnaire			C													M	C				M
	Direct Observation	C		C					C	C	C	C	C	C	C							
Y1-3 (7-9 months)	Blood									C	C	C	C	C	C							
	Urine																					
	Other Physical Sampling			M						C	C	C	C	C	C		M	M				
	Medical Record Review																					
	Interview/ Questionnaire			C													M	C				M
	Direct Observation	C							C	C	C	C	C	C	C							

Table 2.0 Measurement Methods and Timeline for Sampling for Hypotheses[†]

All Participants

(M = Mother; F = Biological Father; C = Index Child; A = Other Adult) *** = Preconception measure would be preferable, if available.**

	Priority Outcome	Pregnancy Outcomes		Neurobehavorial Development			Injury			Asthma						Obesity and Altered Physical Development						
Lifestage	**Method**	**1.1**	**1.2**	**2.1**	**2.2**	**2.3**	**3.1****	**3.2****	**3.3**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**
Y1-4 (10-12 months)	Blood						C			C	C	C	C	C	C			C				C
	Urine						C															
	Other Physical Sampling			M						C	C	C	C	C	C		M					
	Medical Record Review																C	M				
	Interview/ Questionnaire			CA			CA										MC	C				M
	Direct Observation	C							C	C	C	C	C	C	C		C	C				
Y1 (13-18 months)	Blood									C	C	C	C	C	C							
	Urine									C	C	C	C	C	C							
	Other Physical Sampling									C	C	C	C	C	C		M					
	Medical Record Review									C	C	C	C	C	C							
	Interview/ Questionnaire			A				MFA	MFA	C	C	C	C	C	C		C					
	Direct Observation								C													

Table 2.0 Measurement Methods and Timeline for Sampling for Hypotheses†

All Participants

(M = Mother; F = Biological Father; C = Index Child; A = Other Adult) *** = Preconception measure would be preferable, if available.**

	Priority Outcome	Pregnancy Outcomes		Neurobehavorial Development			Injury			Asthma						Obesity and Altered Physical Development						
Lifestage	**Method**	**1.1**	**1.2**	**2.1**	**2.2**	**2.3**	**3.1****	**3.2****	**3.3**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**
Y2 (19-24 months)	Blood						C			C	C	C	C	C	C	C			C	C	C	C
	Urine			C			C			C	C	C	C	C	C							
	Other Physical Sampling									C	C	C	C	C	C			M				
	Medical Record Review	C					C	C	C	C	C	C	C	C	C							
	Interview/ Questionnaire			A			CA	MFA	MFA	C	C	C	C	C	C			C	C	MFC	MFC	C
	Direct Observation			C	C				C										C	C	C	
Y3	Blood						C			C	C	C	C	C	C							
	Urine			C			C			C	C	C	C	C	C							
	Other Physical Sampling									C	C	C	C	C	C							
	Medical Record Review									C	C	C	C	C	C							
	Interview/ Questionnaire			C			C	MFA	MFA	C	C	C	C	C	C			C				
	Direct Observation			C					C													

Table 2.0 Measurement Methods and Timeline for Sampling for Hypotheses†

All Participants

(M = Mother; F = Biological Father; C = Index Child; A = Other Adult) *** = Preconception measure would be preferable, if available.**

	Priority Outcome	Pregnancy Outcomes		Neurobehavorial Development			Injury			Asthma						Obesity and Altered Physical Development						
Lifestage	**Method**	**1.1**	**1.2**	**2.1**	**2.2**	**2.3**	**3.1****	**3.2****	**3.3**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**
Y4	Blood						C															C
	Urine			C			C															
	Other Physical Sampling																					
	Medical Record Review																					
	Interview/ Questionnaire			A			CA	MFA	MFA													
	Direct Observation			C																		
Y5	Blood						C									C			C	C	C	C
	Urine			C			C															
	Other Physical Sampling					C																
	Medical Record Review	C				C	C	C									C					
	Interview/ Questionnaire			A		C	CA	MFA	MFA								C	C	C	MFC	MFC	
	Direct Observation			C		C			C								C	C	C	C	C	

Table 2.0 Measurement Methods and Timeline for Sampling for Hypotheses[†]

All Participants

(M = Mother; F = Biological Father; C = Index Child; A = Other Adult) *** = Preconception measure would be preferable, if available.**

	Priority Outcome	Pregnancy Outcomes		Neurobehavorial Development			Injury			Asthma						Obesity and Altered Physical Development						
Lifestage	**Method**	**1.1**	**1.2**	**2.1**	**2.2**	**2.3**	**3.1****	**3.2****	**3.3**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**
Y6	Blood									C	C	C	C	C	C							
	Urine			C						C	C	C	C	C	C							
	Other Physical Sampling									C	C	C	C	C	C							
	Medical Record Review									C	C	C	C	C	C							
	Interview/ Questionnaire			A						C	C	C	C	C	C							
	Direct Observation			C																		C
Y7	Blood																					
	Urine			C																		
	Other Physical Sampling									C	C	C	C	C	C							
	Medical Record Review									C	C	C	C	C	C							
	Interview/ Questionnaire			C						C	C	C	C	C	C							
	Direct Observation			C	C																	C

Table 2.0 Measurement Methods and Timeline for Sampling for Hypotheses†

All Participants

(M = Mother; F = Biological Father; C = Index Child; A = Other Adult) *** = Preconception measure would be preferable, if available.**

	Priority Outcome	Pregnancy Outcomes		Neurobehavorial Development			Injury			Asthma						Obesity and Altered Physical Development						
Lifestage	**Method**	**1.1**	**1.2**	**2.1**	**2.2**	**2.3**	**3.1****	**3.2****	**3.3**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**
Y8	Blood																					
	Urine																					C*
	Other Physical Sampling																					
	Medical Record Review																					
	Interview/ Questionnaire																					C*
	Direct Observation																					C*
Y10	Blood						C			C	C	C	C	C	C	C			C	C	C	
(This lifestage represents children aged 9-12)	Urine						C			C	C	C	C	C	C							C*
	Other Physical Sampling					C				C	C	C	C	C	C							
Most likely only need to sample once during this period to satisfy most hypotheses with the exception of 5.7	Medical Record Review	C				C	C	C	C	C	C	C	C	C	C		C					
	Interview/ Questionnaire			C		C	C	MFC	MFC	C	C	C	C	C	C		C	C	C	MFC	MFC	C*
	Direct Observation			C		C			C								C	C	C	C	C	C*

Table 2.0 Measurement Methods and Timeline for Sampling for Hypotheses†

All Participants

(M = Mother; F = Biological Father; C = Index Child; A = Other Adult) *** = Preconception measure would be preferable, if available.**

	Priority Outcome	Pregnancy Outcomes		Neurobehavorial Development			Injury			Asthma						Obesity and Altered Physical Development						
Lifestage	**Method**	**1.1**	**1.2**	**2.1**	**2.2**	**2.3**	**3.1****	**3.2****	**3.3**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**
Y15 **(This lifestage represents children aged 13-17)** **Most likely only need to sample once during this period to satisfy most hypotheses with the exception of 5.7**	Blood						C			C	C	C	C	C	C	C			C	C	C	
	Urine						C															C*
	Other Physical Sampling					C				C	C	C	C	C	C							
	Medical Record Review	C				C	C	C	C	C	C	C	C	C	C		C					
	Interview/ Questionnaire			C		C	C	MFC	MFC	C	C	C	C	C	C		C	C	C	MFC	MFC	C*
	Direct Observation			C		C											C	C	C	C	C	C*
Y20 **(This lifestage represents children aged 18-21)** **Most likely only need to sample once during this period to satisfy most hypotheses with the exception of 5.7**	Blood						C			C	C	C	C	C	C	C			C	C	C	
	Urine						C															C*
	Other Physical Sampling					C				C	C	C	C	C	C							
	Medical Record Review	C				C	C	C	C	C	C	C	C	C	C		C					
	Interview/ Questionnaire			C		C	C	MFC	MFC	C	C	C	C	C	C		C	C	C	MFC	MFC	C*
	Direct Observation			C		C											C	C	C	C	C	C*

† This table contains approximations of the measures that will be used in NCS.
**** Hypotheses 3.1 and 3.2 were recently eliminated by the ICC but are currently being further evaluated and possibly strengthened for consideration as NCS hypotheses.**

Table 3.0 Summary of Measurement Methods and Timeline for Sampling for Priority Outcomes†

All Participants
(M = Mother; F = Biological Father; C = Index Child)
*** = Preconception measure would be preferable, if available**

Lifestage	Method	Priority Outcome 1	2	3	4	5
Preconception	Blood	M*	M*	M*		M*
	Urine		M*	M*		
	Other Physical Samples	M*				
	Medical Record Review					
	Interview/ Questionnaire					M*
	Direct Observation	M*				
1st Trimester	Blood	MF	MF	M	MF	MF
	Urine		M	M	M	M
	Other Physical Samples	M	MF			
	Medical Record Review	MF	M			
	Interview/ Questionnaire	MF	MF	MF	MF	MF
	Direct Observation	M				MF
2nd Trimester	Blood	M	M	M	MF	M
	Urine		M	M	M	M
	Other Physical Samples	M	M			
	Medical Record Review	M		M		M
	Interview/ Questionnaire	M	M	M	MF	MF
	Direct Observation	M	C			M

Priority Outcomes
1 = birth defects and preterm birth
2 = altered neurobehavioral development
3 = injury
4 = asthma
5 = obesity and altered physical development

Table 3.0 Summary of Measurement Methods and Timeline for Sampling for Priority Outcomes†

All Participants
(M = Mother; F = Biological Father; C = Index Child)
*** = Preconception measure would be preferable, if available**

Lifestage	Method	Priority Outcome 1	2	3	4	5
3rd Trimester	Blood	M	M	M	MF	M
	Urine		M	M	M	M
	Other Physical Samples	M	M			
	Medical Record Review	M		M		M
	Interview/ Questionnaire	M	M	M	MF	M
	Direct Observation	M	C			M
Birth	Blood	M	MC		MF	M
	Urine					
	Other Physical Samples	C	MC		M	M
	Medical Record Review	C	M			
	Interview/ Questionnaire			MF	MF	MF
	Direct Observation	C	C	C		MC
Y1 -1	Blood				C	MC
(0-3 months)	Urine		M			MC
	Other Physical Samples					
	Medical Record Review					
	Interview/ Questionnaire		C			MC
	Direct Observation	C		C	C	

Priority Outcomes
1 = birth defects and preterm birth
2 = altered neurobehavioral development
3 = injury
4 = asthma
5 = obesity and altered physical development

Table 3.0 Summary of Measurement Methods and Timeline for Sampling for Priority Outcomes†

All Participants
(M = Mother; F = Biological Father; C = Index Child)
*** = Preconception measure would be preferable, if available**

Lifestage	Method	Priority Outcome 1	2	3	4	5
Y1-2	Blood				C	
(4-6 months)	Urine					
	Other Physical Samples		M			M
	Medical Record Review					M
	Interview/ Questionnaire		C			MC
	Direct Observation	C	C	C	C	
Y1-3	Blood				C	
(7-9 months)	Urine					
	Other Physical Samples		M		C	M
	Medical Record Review					
	Interview/ Questionnaire		C			MC
	Direct Observation	C		C	C	
Y1-4	Blood			C	C	C
(10-12 months)	Urine			C		
	Other Physical Samples		M		C	M
	Medical Record Review					MC
	Interview/ Questionnaire		C	C		MC
	Direct Observation	C			C	C

Priority Outcomes
1 = birth defects and preterm birth
2 = altered neurobehavioral development
3 = injury
4 = asthma
5 = obesity and altered physical development

Table 3.0 Summary of Measurement Methods and Timeline for Sampling for Priority Outcomes†

All Participants
(M = Mother; F = Biological Father; C = Index Child)
*** = Preconception measure would be preferable, if available**

Lifestage	Method	Priority Outcome 1	2	3	4	5
Y1	Blood				C	
(13-18 months)	Urine				C	
	Other Physical Samples				C	M
	Medical Record Review				C	
	Interview/ Questionnaire		C	MFC	C	C
	Direct Observation			C		
Y2	Blood			C	C	C
(19-24 months)	Urine		C	C	C	
	Other Physical Samples				C	M
	Medical Record Review	C		C	C	
	Interview/ Questionnaire		C	MFC	C	MFC
	Direct Observation		C	C		C
Y3	Blood			C	C	
	Urine		C	C	C	
	Other Physical Samples				C	
	Medical Record Review				C	
	Interview/ Questionnaire		C	MFC	C	C
	Direct Observation		C	C		

Priority Outcomes
1 = birth defects and preterm birth
2 = altered neurobehavioral development
3 = injury
4 = asthma
5 = obesity and altered physical development

Table 3.0 Summary of Measurement Methods and Timeline for Sampling for Priority Outcomes†

All Participants
(M = Mother; F = Biological Father; C = Index Child)
*** = Preconception measure would be preferable, if available**

Lifestage	Method	Priority Outcome 1	2	3	4	5
Y4	Blood			C		C
	Urine		C	C		
	Other Physical Samples					
	Medical Record Review					
	Interview/ Questionnaire		C	MFC		
	Direct Observation		C			
Y5	Blood			C		C
	Urine		C	C		
	Other Physical Samples		C			
	Medical Record Review	C	C	C		C
	Interview/ Questionnaire		C	MFC		MFC
	Direct Observation		C	C		C
Y6	Blood				C	
	Urine		C		C	
	Other Physical Samples				C	
	Medical Record Review				C	
	Interview/ Questionnaire		C		C	
	Direct Observation		C			C

Priority Outcomes
1 = birth defects and preterm birth
2 = altered neurobehavioral development
3 = injury
4 = asthma
5 = obesity and altered physical development

Table 3.0 Summary of Measurement Methods and Timeline for Sampling for Priority Outcomes†

All Participants
(M = Mother; F = Biological Father; C = Index Child)
*** = Preconception measure would be preferable, if available**

Lifestage	Method	Priority Outcome 1	2	3	4	5
Y7	Blood					
	Urine		C			
	Other Physical Samples				C	
	Medical Record Review				C	
	Interview/ Questionnaire		C		C	
	Direct Observation		C			C
Y8	Blood					
	Urine					C*
	Other Physical Samples					
	Medical Record Review					
	Interview/ Questionnaire					C*
	Direct Observation					C*
Y10	Blood			C	C	C
	Urine			C	C	C*
	Other Physical Samples		C		C	
	Medical Record Review	C	C	C	C	C
	Interview/ Questionnaire		C	MFC	C	C
	Direct Observation		C	C		C

Priority Outcomes
1 = birth defects and preterm birth
2 = altered neurobehavioral development
3 = injury
4 = asthma
5 = obesity and altered physical development

Table 3.0 Summary of Measurement Methods and Timeline for Sampling for Priority Outcomes†

All Participants
(M = Mother; F = Biological Father; C = Index Child)
*** = Preconception measure would be preferable, if available**

Lifestage	Method	Priority Outcome 1	2	3	4	5
Y15	Blood			C	C	C
	Urine			C	C	C
	Other Physical Samples		C		C	
	Medical Record Review	C	C	C	C	C
	Interview/ Questionnaire		C	MFC	C	MFC
	Direct Observation		C			C
Y20	Blood			C	C	C
	Urine			C	C	C
	Other Physical Samples		C		C	
	Medical Record Review	C	C	C	C	C
	Interview/ Questionnaire		C	MFC	C	MFC
	Direct Observation		C			C

† This table contains approximations of the measures that will be used in NCS.

Priority Outcomes
1 = birth defects and preterm birth
2 = altered neurobehavioral development
3 = injury
4 = asthma
5 = obesity and altered physical development

References

1. Undesirable outcomes of pregnancy: birth defects and preterm birth

American Dental Association. http://www.ada.org/public/topics/gum_disease_faq.asp, Accessed: January, 2004.

Andrews, W.W., Hauth, J.C., and Goldenberg, R.L. (2000). Infection and preterm birth. *Am J Perinatol*, 17:357-65.

Becerra, J.E., Khoury, M.J., Cordero, J.F., and Erickson, J.D. (1990). Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. *Pediatrics*, 85(1):1-9.

Casson, I.F., Clarke, C.A., Howard, C.V., McKendrick, O., Pennycook, S., Pharoah, P.O., et al. (1997). Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. *BMJ*, 315(7103):275-278.

Centers for Disease Control and Prevention. National diabetes fact sheet. http://www. Cdc.gov/diabetes/pubs/estimates/htm.

Centers for Disease Control and Prevention. Health, United States, 2003. http://www.cdc/gov/nchs/.

Copper, R., Goldenberg, R., Das, A., Elder, N., Swain, M., Norman, G., Ramsey, R., Cotroneo, P., Collins, B., Johnson, F., Jones, P., and Meier, A. (1996). The preterm prediction study: Maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. *Am J Obstet Gynecol*, 175: 1286-1292.

Eriksson, U.J. (1999). Oxidative DNA damage and embryo development. *Nat Med*, 5(7):715.

Eriksson, U.J., Borg, L.A., Cederberg, J., Nordstrand, H., Siman, C.M., Wentzel, C., et al. (2000). Pathogenesis of diabetes-induced congenital malformations. *Ups J Med Sci*, 105(2):53-84.

Gitau, R., Cameron, A., Fisk, N., and Glover, V. (1998). Fetal exposure to maternal cortisol. *The Lancet*, 352:707-708.

Goldenberg., R.L., Hauth, J.C., and Andrews, W.W. (2000). Intrauterine infection and preterm delivery. *New Engl J Med*, 18;342(20):150-7.

Goldenberg, R.L., Thom, E., Moawad, A.H., Johnson, F., Roberts, J., Caritis, S.N., et al. (1996). The preterm prediction study: fetal fibronectin, bacterial vaginosis, and peripartum infection. *Obstet Gynecol*, 87:656-60.

Hillier, S.L., Martius, J., Krohn, M., Kiviat, N., Holmes, K.K., Eschenbach, D.A. (1988). A case-control study of chorioamnionic infection and histologic chorioamionitis in prematurity. *New Engl J Med*, 319:972-8.

Kucera, J. (1971). Rate and type of congenital anomalies among offspring of diabetic women. *J Reprod Med*, 7(2):73-82.

Martinez-Frias, M.L., Bermejo, E., Rodriguez-Pinilla, E., Prieto, L., and Frias, J.L. (1998). Epidemiological analysis of outcomes of pregnancy in gestational diabetic mothers. *Am J Med Genet*, 78(2):140-145.

Nelson, K.B., Grether, J.K., Dambrosia, J.M., Dickens, B., and Phillips, T.M. (2000). Cytokine concentrations of neonatal blood of preterm children with cerebral palsy (CP). *Am J Obstet Gynecol*, 182:S47.

Offenbacher, S., Lieff, S., Boggress, K.A., et al. (2001). Part I: Obstetric outcome of prematurity and growth restriction. *Annals of Peridontology*, 6:164-174.

Schaefer, U.M., Songster, G., Xiang, A., Berkowitz, K., Buchanan, T.A., and Kjos, S.L. (1997). Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. *Am J Obstet Gynecol*, 177(5):1165-1171.

Tikkanen, J., and Heinonen, O.P. (1992). Risk factors for atrial septal defect. *Eur J Epidemiol*, 8(4):509-15.

2. Altered neurobehavioral development, developmental disabilities, and psychiatric outcomes.

Bejar, R., Wozniak, P., Allard, M., Benirschke, K., Vaucher, Y., Coen, R., Berry, C., Schragg, P., Villegas, I., and Resnik, R. (1988). Antenatal origin of neurologic damage in newborn infants. I. Preterm infants. *Am J Obstet Gynecol*, 159:357-63.

Bresnahan, M.A., Brown, A.S., Schaefer, C.A., Begg, M.D., Wyatt, R.J., and Susser, E.S. (2000). Incidence and cumulative risk of treated schizophrenia in the prenatal determinants of schizophrenia study. *Schizophr Bull*, 26(2):297-308.

Buka, S.L., Tsaung, M.T., Torrey, E.F., Klebanoff, M.A., Bernstein, D., and Yolken, R.H. (2001a). Maternal infections and subsequent psychosis among offspring. *Arch Gen Psychiatry*, 58(11):1032-7.

Buka, S.L., Tsaung, M.T., Torrey, E.F., Klebanoff, M.A., Wagner, R.L., and Yolken, R.H. (2001b). Maternal cytokine levels during pregnancy and adult psuchosis. *Brain Behav Immun, 15(4):411-20*.

Eskenazi, B., Bradman, A., and Castoria, R. (1999). Exposures of children to organophosphate pesticides and their potential adverse health effects. *Environ Health Perspect*, 107(3):409-419.

Grether, J.K., and Nelson, K.B. (1997). Maternal infection and cerebral palsy in infants of normal birth weight. *JAMA*, 278(3):207-11.

Grether, J.K., Nelson, K.B., Dambrosia, J.M., and Phillips, T.M. (1999). Interferons and cerebral palsy. *J Pediatr*, 134:324-334.

Gunnar, M., Porter, F., Wolf, C., Rigatuso, J., and Larson, M. (1995). Neonatal stress reactivity: Predictions to later emotional temperament. *Child Dev*, 66:1-13.

Heim, C., and Nemeroff, C. (1999). The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biological Psychiatry*, 46:1509-1522.

Lou, H.C., Hansen, D., Nordentoft, N., Pryds, O., Jensen, F., Nim, J., and Hemmingsen, R. (1994). Prenatal stressors of human life affect fetal brain development. *Dev Med Child Neurol*, 36:826-832.

Mattson, S.N., Riley, E.P., Delis, D.C., et al. (1996). Verbal learning and memory in children with fetal alcohol syndrome. *Alcohol Clin Exp Res*, 20(5):810-16.

Mendola, P., et al. (2002). Environmental factors associated with a spectrum of neuropsychological deficits. *Ment Retard Dev Disabil Res Rev*, 8:188-197.

Myers, G.J., and Davidson, P.W. (2000). Does methylmercury have a role in causing developmental disabilities in children? *Environ Health Perspectives*, 108(3):413-420.

Nelson, K.B., Dambrosia, J.M., Grether, J.K., and Phillips, T.M. (1998). Neonatal cytokines and coagulation factors in children with cerebral palsy. *Ann Neurol*, 44:665-675.

Nelson, K.B., and Willoughby, R.E. (2002). Overview: infection during pregnancy and neurologic outcome in the child. *Ment Retard Dev Disabil Res Rev*, 8(1):1-2.

Ribas-Fito, N., Sala, M., Kovgevinas, M., and Sunyer, J. (2001). Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review. *J Epidemiol and Comm Health*, 55:537-546.

Rodier, P.M., and Hyman, S.L. (1998). Early environmental factors in autism. *Ment Retard Dev Disabil Rev*, 4(2):121-128.

Roebuck, T.M., Mattson, S.N., Riley, E.P. (1999). Behavioral and psychosocial profiles of alcohol-exposed children. *Alcohol Clin Exp Res*, 23(6):1070-1076.

Yoon, B.H., Jun, J.K., Romero, R., et al. (1997). Amniotic fluid inflammatory cytokines (interleukin-6, interleukin-1β, and tumor necrosis factor-α), neonatal brain white matter lesions, and cerebral palsy. *Am J Obstet Gynecol*, 177:19-26.

Yoon, B.H., Kim, C.J., Romero, R., et al. (1997). Experimentally induced intrauterine infection causes fetal brain white matter lesions in rabbits. *Am J Obstet Gynecol*, 177:797-802.

Yoon, B.H., Park, J.S., Romero, R., et al. (1999). Intraamniotic inflammation and the development of cerebral palsy at three years of age. *Am J Obstet Gynecol*, 180:S2.

Yoon, B.H., Romero, R., Kim, M., et al. (2001). Elevated amniotic fluid matrix metalloproteinase-8 and the subsequent development of cerebral palsy. *Am J Obstet Gynecol*, 184:S3.

Wu, Y.W., and Colford, J.M. (2000). Chorioamnionitis as a risk factor for cerebral palsy: a meta-analysis. *JAMA*, 284:1471-24.

3. Injury

Anderson, V.A., et al. (2001). Predictors of acute child and family outcome following traumatic brain injury in children. *Pediatr Neurosurgery*, 34:138-48.

Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. (1999). Facts on Adolescent Injury. Available online at http://www.cdc.gov/ncipc/factsheets/adoles.htm.

Cummins, S.K., and Jackson, R.J. (2001). The built environment and children's health. *Children's Environmental Health*, 48:1241-1252.

Hawley, C.A., et al. (2002). Children's brain injury: a postal follow-up of 525 children from one health region in the UK. *Brain Injury*, 16:969-85.

Laflamme, L., and Menkel, E. (2001). Pupil injury risks as a function of physical and psychosocial environmental problems experienced at school. *Inj Prev*, 2:146-9.

Miller, T.R., Romano, E.O., and Spicer, R.S. (2000). The cost of childhood unintentional injuries and the value of prevention. *The Future of Children*, 10:137-163.

Salcido, R., and Costich, J.F. (1992). Recurrent traumatic brain injury. *Brain Injury*, 6:293-8.

Stiffman, M.N., Schnitzer, P.G., Adam, P., Kruse, R.L., and Ewigman, B.G. (2002). Household composition and risk of fatal child maltreatment. *Pediatrics*, 109:615-621.

Stoddard, F.J., and Saxe, G. (2001). Ten-year research review of physical injuries. *J Am Acad Child Adolesc Psychiatry*, 40(10):1128-1145.

4. Asthma

Abbey, D.E., Ostro, B.E., Petersen, F., and Burchette, R.J. (1995). Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$) and other air pollutants. *J Expos Anal Environ Epidemiol*, 5: 137-159.

Boland, S., Baeza-Squiban, A., Fournier, T., and Houcine, O. (1999). Diesel exhaust particles are taken up by human airway epithelial cells in vitro and alter cytokine production. *Am J Physiol Lung Cell Mol Physiol*, 20(4):L604-L613.

Carter, M.C., Perzanowski, M.S., Raymond, A., and Platts-Mills, T.A.E. (2001). Home intervention in the treatment of asthma among inner-city children. *J Allergy Clin Immunol*, 108:732-737.

Croner, S., and Kjellman, N.-I.M. (1992). Natural history of bronchial asthma in childhood: a prospective study from birth up to 12-14 years of age. *Allergy*, 47:150-157.

Dobbin, J.P., et al. (1991). Cytokine production and lymphocyte transformation during stress. *Brain Behav Immun*, 5:339-348.

Droste, J.H., Wieringa, M.H., Weyler, J.J., Nelen, V.J., Vermiere, P.A., and Van Bevers, H.P. (2000). Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exper Allergy*, 30:1547-53.

Eggleston, P.A., Buckley, P.N., Breysse, T.J., Wills-Karp, M., Kleeberger, S.R., and Jaakkola, J.J. (1999). The environment and asthma in US inner cities. *Environ Health Perspect*, 107(3 suppl):439-450.

Finn, P.W., et al. (2000). Children at risk for asthma: home allergen levels, lymphocyte proliferation, and wheeze. *J Allergy Clin Immunol*, 105(5):933-42.

Gehring, U., et al. (2002). House dust endotoxin and allergic sensitization in children. *Am J Respiratory Critical Care Medicine*, 166:939-944.

Gergen, P.J. (2001). Environmental tobacco smoke as a risk factor for respiratory disease in children. *Respir Physiol*, 128(1):39-46.

Gottlieb, D.J., Beiser, A.S., and O'Connor, G.T. (1995). Poverty, race, and medication use are correlates of asthma hospitalization rates: a small area analysis of Boston. *Chest*, 108:28-35.

Herbert, T., and Cohen, S. (1993). Stress and immunity in humans: a meta-analytic review. *Psychosom Med*, 55:364-379.

Homer, C.J., et al. (1996). Does quality of care affect rates of hospitalization for childhood asthma? *Pediatrics*, 98:18-23.

Lanphear, B.P., Kahn, R.S., Berger, O., Auinger, P., Bortnick, S.M., and Nahhas, R.W. (2001). Contribution of residential exposures to asthma in U.S. children and adolescents. *Pediatrics*, 107(6):E98.

Liu, A.H. (2002). Endotoxin exposure in allergy and asthma: reconciling a paradox. *J Clin Immunol*, 109(3):379-92.

London, S.J., Gauderman, W.J., Avol, E., Rappaport, E.B., and Peters, J.M. Family history and the risk of early-onset persistent, early-onsete transient, and late-onset asthma. *Epidemiology*, 12(5):577-83.

Marder, D., Tangonski, P., Orris, P., Persky, V., and Addington, W. (1992). Effect of racial and socioeconomic factors on asthma mortality in Chicago. *Chest*, 10(6):426S-429S.

Martinez, F.D. (2002). Development of wheezing disorders and asthma in preschool children. *Pediatrics*, 109(2 Suppl):362-7.

Mattes, J., and Karmaus, W. (1999). The use of antibiotics in the first year of life and development of asthma: which comes first? *Clin and Exper Allergy*, 29:729-32.

McEwen, B.S. (1998). Protective and damaging effects of stress mediators. *N Engl J Med*, 338:171-179.

Nel, A.E., Diaz Sanchez, D., Ng, D., Hiura, T., and Saxon, A. (1998). Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system. *J Allergy Clin Immunol*, 102: 539-54.

Platts-Mills, T.A. (2001). Con: The increase in asthma cannot be ascribed to cleanliness. Letter, Comment. *Am J Respir Crit Care Med*, 164(7):1107-8; discussion 1108-9.

Schwartz, J. (1993). Particulate air pollution and chronic respiratory disease. *Environ Res*, 62: 7-13.

Sears, M.R., et al. (1991). Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med*, 325(15):1067-71.

Sherman, C.B., et al. (1990). Early childhood predictors of asthma. *Am J Epidemiol*, 132(1):83-95.

Sporik, R. (2001). Allergen exposure and the development of asthma. *Thorax*, 56 (2 Suppl):ii58-63.

Sunyer, J. (2001). Urban air pollution and chronic obstructive pulmonary disease: A review. *Eur Respir J*, 17:1024-33.

von Mutius, E. (2001) Pro: the increase in asthma can be ascribed to cleanliness. [See Comments.] *Am J Respir Crit Care Med*, 164(7):1106-7; discussion 1108-9.

Weitzman, M., Gortmaker, S., Sobol, A. (1990). Racial, social, environmental risks for childhood asthma. *Am J Dis Child*, 144:1189-1194.

Wright, R.J., Cohen, S., Carey, V., Weiss, S.T., and Gold, D.R. (2002). Parental stress as a predictor of wheezing in infancy: a prospective birth-cohort study. *Am J Respir Crit Med*, 165(3):358-65.

5. Obesity and altered physical development.

Birch, L.L., and Fisher, J.O. (1998). Development of eating behaviors among children and adolescents. *Pediatrics*, 101(3 pt 2):539-49.

Brand-Miller, J.C., Holt, S.H., Pawlak, D.B., and McMillan, J. (2002). Glycemic index and obesity. *Am J Clin Nutr*, 76(1):281S-5S.

Breier, B.H., Vickers, M.H., Ikenasio, B.A., Chan, K.Y., and Wong, W.P.S. (2001). Fetal programming of appetite and obesity. *Mol Cell Endocrinol*, 185(1-2):73-79.

Colditz, G.A. (1992). Economic costs of obesity. *Am J Clin Nutr*, 55(2):S503-S507.

Dietz, W.H. (2001). Breastfeeding may help prevent childhood overweight. *JAMA*, 285(19):2506-7.

Freeman, D.S., Khan, L.K., Dietz, W.H., Srinivasan, S.R., and Berenson, G.S. (2001). Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. *Pediatrics*, 108(3):712-8.

Gillman, J.K., Rifas-Shiman, S.L., Camargo, C.A. Jr., Berkey, C.S., Frazier, A.L., Rockett, H.R., Field, A.E., and Colditz, G.A. (2001). Risk of overweight among adolescents who were breastfed as infants. *JAMA*, 285(19):2461-7.

Handy, S.L., Boarnet, M.G., Ewing, R., and Killingsworth, R.E. (2002). How the built environment affects physical activity: views from urban planning. *Am J Prev Med*, 23(2 Suppl):64-73.

Hediger, M.L., Overpeck, M.D., Kuczmarski, R.J., and Ruan, W.J. (2001). Association between infant breastfeeding and overweight in young children. *JAMA*, 285(19):2453-60.

Kohl, H.W. 3rd, and Hobbs, K.E. (1998). Development of physical activity behaviors among children and adolescents. *Pediatrics*, 101 (3 Pt 2):549-54.

Kuszmarski, R.J., Flegal, K.M., Campbell, S.M., and Johnson, C.L. (1994). Increasing prevalence of overweight among US adults. National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA*, 272(3):205-11.

Mokad, A.H., Serdula, M.K., Dietz, W.H., Bowman, B.A., Marks, J.S., and Koplan, J.P. (1999). The spread of the obesity epidemic in the United States, 1991-1998. *JAMA*, 282(16):1519-22.

Ogden, C.L., Flegal, K.M., Carroll, M.D., and Johnson, C.L. (2002). Prevalence and trends in overweight among US children and adolescents, 1999-2000. *JAMA*, 288(14):1728-32.

Ong, K.K., Ahmed, M.L., Emmett, P.M., Preece, M.A., and Dunger, D.B. (2000). Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ*, 320(7240):967-71.

Parsons, T.J., Power, C., Logan, S., and Summerbell, C.D. (1999). Childhood predictors of adult obesity: a systematic review. *Int J Obes Relat Metab Disord*, 23(8 Suppl):S1-107.

Serdula, M.K., Ivery, D., Coates, R.J., Freedman, D.S., Williamson, D.F., and Byers, T. (1993). Do obese children become obese adults? A review of the literature. *Prev med*, 22(2):167-77.

von Kries, R, Koletzko, B., Sauerwald, T., von Murtius, E., Barnert, D., Grunert, V., and von Voss, H. (1999). Breastfeeding and obesity: cross-sectional study. *BMJ*, 319(7203):147-50.

Whitaker, R.C., and Dietz, W.H. (1998). Role of the prenatal environment in the development of obesity. *J Pediatr*, 132(5):768-76.

6. Additional references associated with this report.

Arroyo, C. (2003) "Mixed Effects Models for Multiple Outcomes: Application for Physical Activity Data." Ph.D. Thesis, Harvard School of Public Health, Department of Biostatistics.

Loecke, D (2003) "Mixed Effects Mean Score Method for Auxiliary and Missing Covariate Data in Longitudinal Regression Models." Ph.D. Thesis, Harvard School of Public Health, Department of Biostatistics.

Park, S. and Ryan, L. (2003) “Optimal Design for Studies Involving Replicate Exposure Measurements Subject to Short and Long Term Variation.” Technical Report, Harvard School of Public Health, Department of Biostatistics.

Roberts, K (2003) “Latent Variable Models for Exposure Measurement Error in Environmental Studies.” Ph.D. Thesis, Harvard School of Public Health, Department of Biostatistics.

Ryan, L., Loecke, D., Roberts, K., Park, S. Arroyo, C., Strauss, W.J. “Development of Exposure Assessment Study Design for the National Children’s Study: Optimal Design Methods and Statistical Analysis Methods.” Technical Report submitted by Battelle to U.S. Environmental Protection Agency, National Exposure Research Laboratory under Task 3 of Task Order 19 on Contract 68-D-99-011, June 2003

Strauss, W.J., Lehman J., Morara, M., Ryan, L., “Development of Exposure Assessment Study Design for the National Children’s Study: Simulation of Exposure and Health Outcome Research Sub-Samples for Guiding Environmental Sampling Design Options.” Technical Report submitted by Battelle to U.S. Environmental Protection Agency, National Exposure Research Laboratory under Task 4 of Task Order 19 on Contract 68-D-99-011, May 2003

Strauss, W.J., Lehman J., Morara, M., Ryan, L., “Development of Exposure Assessment Study Design for the National Children’s Study: Project Overview, Results and Recommendations.” Technical Report submitted by Battelle to U.S. Environmental Protection Agency, National Exposure Research Laboratory under Task 4 of Task Order 19 on Contract 68-D-99-011, May 2003

Strauss, W.J., Lehman, J., Ryan, L., Morara, M., “Development of Exposure Assessment Study Design for the National Children’s Study: Power and Efficiency Analysis.” Technical Report submitted by Battelle to U.S. Environmental Protection Agency, National Exposure Research Laboratory under Task 5 of Task Order 19 on Contract 68-D-99-011, June 2003